NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcranial magnetic stimulation for treating and preventing migraine

Treating and preventing migraine by magnetic stimulation to the brain

Migraine is a severe recurrent headache often associated with nausea, and sensitivity to light and sound. Sometimes it is preceded by an 'aura' (which may include visual disturbances, an imagined unpleasant smell or difficulties with speech).

Transcranial magnetic stimulation can be used during or between migraine attacks. A device is used to deliver a magnetic pulse or pulses to the scalp. The pulse or pulses pass throughout the brain and can stop or reduce the severity of migraine attacks or prevent them from starting.

Introduction

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

Date prepared

This overview was prepared in March 2013.

Procedure name

- Transcranial magnetic stimulation for treating and preventing migraine.

Specialist societies

- Association of British Neurologists.
- British Association for the Study of Headache.

Description

Indications and current treatment

Migraine is a common condition characterised by recurrent, pulsatile, unilateral or bilateral headaches that can last for hours to days and are often accompanied by nausea, and sensitivity to light and sound. Migraine headache may be preceded by an aura, which can include visual or olfactory disturbances, or difficulties with speech (dysphasia). The second edition of International Classification of Headache Disorders (International Headache Society 2004) provides a classification of migraine types.

Current treatment for migraine aims to prevent or stop episodes and manage symptoms with drugs such as triptans, analgesics and anti-emetics (as recommended in Headaches: diagnosis and management of headaches in young people and adults [NICE clinical guideline 150]). Other treatments include nerve blocks, botulinum toxin type A injections (as recommended in Botulinum toxin type A for the prevention of headaches in adults with chronic migraine [NICE technology appraisal guidance 260]) or acupuncture.

What the procedure involves

Transcranial magnetic simulation (TMS) is a non-invasive procedure that aims to treat or prevent migraine episodes in people with acute or chronic migraine (with or without aura). TMS is given using a tabletop or handheld device that delivers a predetermined level of magnetic pulse or pulses to the head.

The device is placed on the scalp and either single (sTMS) or repeated (rTMS) magnetic pulses are delivered. The frequency, intensity, duration and interval times of pulses can be varied. Treatments can be automatically recorded by the device in an integrated headache diary, which can be used to identify headache patterns and trigger factors. Patients may continue to use regular medications, including drugs to prevent migraines.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transcranial magnetic stimulation for treating and preventing migraine. Searches were conducted of the following databases, covering the period from their commencement to 15 March 2013: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

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

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with migraine.
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 332 patients from 2 randomised controlled studies and 3 case series.

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

Table 2 Summary of key efficacy and safety findings on transcranial magnetic stimulation for treating and preventing migraine

Abbreviations used: ICHD, International Classification of Headache Disorders; IHS, International Headache Society; ITT, intention to treat; PDA, personal digital assistant; TMS, single-pulse transcranial magnetic stimulation;

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Lipton RB (2010)[1]
Randomised controlled trial
USA (16 centres)
Recruitment period: 2006-8
Study population: patients with moderate or severe migraine with aura
n=201 (102 sTMS vs 99 sham stimulation)
Age: sTMS mean 38.8 and sham 40 years
Sex: sTMS: 82% (67/82); sham: 77% (63/82) female
Patient selection criteria: 18-70 years, met criteria for migraine with aura (ICHD classification code 1.2.1), 1-8 migraine episodes per month, visual aura preceding for at least 30% of episodes, followed by moderate or severe headache in 90% of migraine attacks.
Exclusion criteria: aura for > 60 minutes, presence of metal implants, headaches due to underlying pathology or trauma, overuse of drugs for headaches, drugs confounding study results.
Technique: In baseline phase, patients were trained to keep an electronic headache diary (PDA) for a month to confirm diagnosis of migraine with aura. In treatment</td>
<td>Number of patients analysed: 164 (82 sTMS and 82 sham) treated at least 1 migraine with aura episode (modified ITT analysis)
2 hours pain-free response for the first treated attack (primary outcome)
Pain-free response rates after 2 h were significantly higher with sTMS 39% (32/82) than with sham stimulation 22% (18/82), for a therapeutic gain of 17% (95% CI 3-31%; p=0.0179).
Sustained pain-free response (with no recurrence and no rescue drug use) rates significantly favoured sTMS at 24 h (29% [24/82] vs 16% [13/82]; p=0.0405) and 48 h (27% [22/82] vs 13% [11/82]; p=0.0327) after treatment.
Relief of migraine associated symptoms at 2 hours after treatment (per-protocol analysis set, p values not given)
<table>
<tr><th></th><th>sTMS (n=70)</th><th>Sham (n=71)</th><th>Mean difference (SE)*</th><th>Upper one sided 95% CI</th></tr>
<tr><td>Photophobia</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Unadjusted</td><td>48 (69%)</td><td>53 (75%)</td><td>-6.1% (7.6)</td><td>6.3%</td></tr>
<tr><td>Adjusted for preventive treatment and baseline photophobia</td><td>48 (69%)</td><td>53 (75%)</td><td>-6.1% (2.1)</td><td>-2.6%***</td></tr>
<tr><td>Phonophobia</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Unadjusted</td><td>36 (51%)</td><td>44 (62%)</td><td>-10.5% (8.3)</td><td>3.0%**</td></tr>
<tr><td>Adjusted for preventive treatment and baseline</td><td>36 (51%)</td><td>44 (62%)</td><td>-10.5% (3.0)</td><td>-5.5%***</td></tr>
</table>
</td>
<td>No device related serious adverse events were reported.
Adverse events within 48 hours*
<table>
<tr><th>Adverse events</th><th>sTMS n=102</th><th>Sham stimulation n n=99</th></tr>
<tr><td>Patients with at least 1 adverse event</td><td>14% (14/102)</td><td>9% (9/99)</td></tr>
<tr><td>At least 1 treatment related adverse event</td><td>5% (5/102)</td><td>2% (2/99)</td></tr>
<tr><td>Total adverse events</td><td>19</td><td>10</td></tr>
<tr><td>Deaths</td><td>0</td><td>0</td></tr>
<tr><td>Headache</td><td>2% (2/102)</td><td>1% (1/99)</td></tr>
<tr><td>Migraine</td><td>0</td><td>2% (2/102)</td></tr>
<tr><td>Sinusitis</td><td>2% (2/102)</td><td>0</td></tr>
<tr><td>Paraesthesia</td><td>0</td><td>2% (2/99)</td></tr>
<tr><td>Severe nausea</td><td>1</td><td>1</td></tr>
</table>
</td>
<td>Follow-up issues:
In treatment phase, 37 did not have an aura attack and were excluded from the analysis.
Study design issues:
A double blinded, randomised, sham controlled parallel group 2 phase study
Individuals who had at least 1 migraine with aura episode were randomised in treatment phase in a 1:1 ratio.
Modified intention to treat and per protocol analyses were performed.
Baseline pain intensity was no pain (30%), mild (40%), moderate (23%), or severe pain (6%).
Global assessment of pain relief was recorded on a 5 point scale ranging from excellent to poor.
Patients were not allowed to use analgesics, antiemetics, triptans, ergots, or other drugs that could confound assessment within the 12 h before treatment.</td>
</tr>
</table>

Abbreviations used: ICHD, International Classification of Headache Disorders; IHS, International Headache Society; ITT, intention to treat; PDA, personal digital assistant; TMS, single-pulse transcranial magnetic stimulation;

Study details

phase, patients were allocated to either active sTMS or identical sham treatment (an inactive identical device was used). Patients applied the sTMS device to the occiput, and administered two 0.9 T magnetic pulses, 30 seconds apart, soon after aura onset (during or within 1 hour) to treat up to 3 attacks of aura over 3 months. Baseline and follow-up (at 30 minutes, 1 h, 2 h, 24 and 48 h) features recorded with the PDA. Baseline pain and symptoms were also recorded. Patients used regular medications including migraine preventive drugs. Rescue drugs were permitted 2 h after treatment.

Follow-up: **48 hours**

Conflict of interest/source of funding: study sponsored and managed by manufacturer (Neuralieve). One author is co-inventor of device and board member of the company. One author contracted as a paid statistician, and one worked as consultant for the publication. 4 authors were consultants to and received research grants from the manufacturer and worked with or advised other device companies. 2 of these hold stocks in Neuralieve.

Key efficacy findings

phonophobia and treatment interaction				
Nausea				
Unadjusted	26 (37%)	28 (39%)	-2.3% (8.2)	11.13%
Adjusted for preventive treatment and baseline nausea	26 (37%)	28 (39%)	-2.3% (2.8)	2.39%**

*difference between the proportion of patients with symptoms at 2 h in each group; ** meets criteria for non-inferiority (<5%), *** meets criteria for non-inferiority (<5%) and superiority (<0%).

Secondary outcomes

	sTMS (n=82)	**Sham (n=82)**	**p value**
No or mild pain 2 hours after treatment	72% (59)	67% (55)	0.4988
Use of rescue drugs-0-48 hours	48% (39)	46% (38)	0.8760
MIDAS* questionnaire change from screening	-4.6 (21.8)	-4.7 921.3)	0.9844

*Migraine disability Assessment Score

There were no significant differences with regard to consistency of pain relief (in episodes, p=0.3441) or global assessment of relief (on a 5 point scale 'poor to excellent', p=0.6833).

Key safety findings

Severe migraine	1	0
Severe headache	1	0

*only events with more than 2% frequency are listed above.

Most adverse events were mild to moderate (headache, migraine, sinusitis and paraesthesia).

None of the patients discontinued the trial because of adverse events.

Comments

Study population issues:

- Treatment groups were similar with respect to frequency of migraine attack and use of preventive medications.
- 97% (196/201) were taking at least one concomitant drug at baseline.

Other issues:

- Results are only applicable for patients with recurrent aura and predictable subsequent headache.

Abbreviations used: ICHD, International Classification of Headache Disorders; IHS, International Headache Society; ITT, intention to treat; PDA, personal digital assistant; TMS, single-pulse transcranial magnetic stimulation;

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Clarke MB (2006)[2]
Case series
Canada (single centre)
Recruitment period: not reported
Study population: patients with migraine (10 had migraine with aura, 25 without aura and 6 had headache with migraine components).
n=42 (21 high intensity stimulation vs 21 low intensity stimulation)
Age: mean 41.42 years
Sex: 86% (36/42) female
Average headache duration: 8.84±14.65 hours; headache pain persistence: 20 min to 10 days; headache frequency: range 1 day to 4 years.
Patient selection criteria: patients with migraine (ICHD-II classification), must live and/or work within 30 minutes of the clinic.
Exclusion criteria: metal in the cranium, cardio/neuro pacemakers, previous seizure activity, neurosurgery or head injury.
Technique: single-pulse TMS was applied using a tabletop clinic based Caldwell Stimulator (model# MES-10). The high intensity group (50% of maximum output) and low intensity group (30% of maximum output) received 2 brief pulses (of 70 ms width) of TMS at 5 seconds</td>
<td>Number of patients analysed: 42

The mean differences between high and low stimulation groups were slight so they were combined into 1 group for comparisons. 42 people had 1 treatment, 50% (22/42) had 2 treatments, 25% (11/42) had 3 treatments.

Pain
Pain decreased by 75% from baseline after treatment with TMS (3.30±0.74 vs 2.49±1.01 [p<0.05])

Improvement in headache*
<table>
<tr><td>Treatment 1 (n=42)</td><td>69%</td></tr>
<tr><td>Treatment 2 (n=22)</td><td>87%</td></tr>
<tr><td>Treatment 3 (n=11)</td><td>82%</td></tr>
</table>
*defined as a decrease in perception of pain of at least 1 level (on a 5 point Likert scale, 5 indicating worst response) and decrease in the number of headaches occurring after TMS.
In individuals with an aura (n=10), relief was 100% and immediate.
The mean time to show improvement was 15.46±6.82 minutes.

Headache recurrence after 24 hours
<table>
<tr><th>Treatments</th><th>None %</th><th>Mild %</th><th>Moderate %</th><th>Severe %</th></tr>
<tr><td>1 (n=42)</td><td>32</td><td>24</td><td>11</td><td>33</td></tr>
<tr><td>2 (n=22)</td><td>29</td><td>16</td><td>8</td><td>46</td></tr>
<tr><td>3 (n=11)</td><td>40</td><td>30</td><td>0</td><td>30</td></tr>
</table>
In patients without aura, 6 were headache free after treatment 1, 8 after treatment 2; 1 after treatment 3 (after 20 minutes).</td>
<td>No adverse side effects reported immediately or 24 hours after treatment.
Slight unsustained dizziness (n=1)
Drowsiness (n=1)
Tired (n=2)
None recurred or required medical attention.

Autonomic nervous system effects (n=32)
<table>
<tr><th></th><th>Pre-stimulation</th><th>Post stimulation</th><th>P value</th></tr>
<tr><td>Mean heart rate (beats /min)</td><td>79.05± 10.27</td><td>72±11.35</td><td>NR</td></tr>
<tr><td>Low-frequency (LF) area (beats /min^2)</td><td>6522±1277</td><td>8315 ±1009</td><td>p<0.001</td></tr>
<tr><td>High-frequency (HF) area (beats /min^2)</td><td>5600±1568</td><td>8755 ±3071</td><td>p<0.001</td></tr>
</table></td>
<td>Study design issues
• Method of randomisation (between low intensity and high intensity groups) not reported.
• Patients and investigators were blinded to intensity of the stimulation.

Study population issues:
• The precipitating factors for migraine were hormonal changes (n=6), stress (n=2), head injury (n=3), and food sensitivities (n=2). In 25 patients it is unknown.
• 14 patients reported onset of headache in the morning, 11 in the afternoon and 17 unable to define a pattern of onset.
• 51 complaints of pain were reported, of these 19 were in the temporal area, 24 in the occipital area and 8 in frontal area of the brain. 9 were in more than 1 area.
• Other symptoms were nausea, double vision, photophobia aura and dizziness.
• 76% patients did not take medications before treatment and 24% post treatment.

Other issues
• Sometimes by the time</td>
</tr>
</table>

Abbreviations used: ICHD, International Classification of Headache Disorders; IHS, International Headache Society; ITT, intention to treat; PDA, personal digital assistant; TMS, single-pulse transcranial magnetic stimulation;

Study details	Key efficacy findings	Key safety findings	Comments
interval over the area of the brain generating the aura or pain. No patient received more than 3 pulses of TMS at any given time. Repeat treatments remained at the initial stimulation intensities. Headache diaries were kept pre and post stimulation. There were no restrictions on medications, which consisted of analgesics, narcotics, antiemetics and/or sedatives. Follow-up: **24 hours** Conflict of interest/source of funding: not reported	**Perception of suffering (assessed by Measuring and Assessing Suffering Questionnaire)** There were no significant differences in total suffering scores between those with pain (n=19) and those without pain (n=23) (2.24±0.54 vs 2.36±0.573).	LF:HF ratio: 1.31±0.51 vs 1.13±0.48, NS	patients came to the clinic, aura disappeared and headache was well established.

Abbreviations used: ICHD, International Classification of Headache Disorders; IHS, International Headache Society; ITT, intention to treat; PDA, personal digital assistant; TMS, single-pulse transcranial magnetic stimulation;

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Teepker M (2009)[3]
Case series (pre-post design)
Germany (single centre)
Recruitment period: not reported
Study population: patients with migraine (14 without aura and 13 with aura)
n=32 (rTMS 14 vs sham 13)
Age: mean 40.62 years
Sex: 81% (22/27) female
Patient selection criteria: patients with migraine according to IHS guidelines, with at least 4 attacks per month, examined by specialist in headache.

Technique: The rTMS group used a tabletop MagPro compact stimulator (with round coil) to apply 2 trains of 500 pulses separated by 1 min at a frequency of 1 Hz for 5 consecutive days. The stimulator intensity was set to visual motor threshold of the dominant hand-2%. The sham stimulation by a figure 8 coil (Medtronic) produced same sound and sensory feedback.

Follow-up: 8 weeks
Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 27
Migraine attacks
In the rTMS group, the number of migraine attacks during 8 weeks was significantly reduced from 9.36±2.82 attacks to 6.79±4.28 attacks (p=0.007). In the sham group, the number of migraine attacks also decreased (p=0.216). Comparing the effects between rTMS and sham groups, no significant difference was seen (p=0.698).

Migraine days
There was a significant reduction of migraine days during 8 weeks in both rTMS and sham groups (from 17.69±11.63 days to 13.15±9.27 days, p=0.012; from 14.36±5.07 days to 9.50±6.80 days, p=0.006). Comparing the effects between rTMS and sham groups, no significant difference was seen (p=0.884).

Migraine hours
The rTMS group showed a significant reduction of migraine hours during 8 weeks from 125.93±80.31 h to 85.36±72.27h, p=0.035; no significance in the sham group (p=0.080) or between the sham and rTMS groups (p=0.846).

Migraine- mean pain intensity
In the rTMS group, mean pain intensity during 8 weeks changed minimally from 6.26±1.33 to 6.11±1.26, p=0.455; in the sham group, from 5.52±1.72 to 5.17±2.51, p=0.839, or between the rTMS and sham groups were not significant (p=0.942).

Migraine- use of analgesics
In the rTMS group, the intake of analgesics during 8 weeks changed from 14.21±10.13 pills to 12.50±14.65 pills, p=0.232; in the sham group, from 15.15±11.24 pills to 11.81±9.89, p=0.094, or between the rTMS and sham groups were not significant (p=0.577).</td>
<td>Side effects
<table>
<tr><th></th><th>rTMS n=14</th><th>Sham n=13</th></tr>
<tr><td>During treatment</td><td></td><td></td></tr>
<tr><td>Visual motor threshold is uncomfortable</td><td>5</td><td>4</td></tr>
<tr><td>Sitting long-lasting and uncomfortable</td><td>1</td><td>1</td></tr>
<tr><td>Sleepiness</td><td>1</td><td>1</td></tr>
<tr><td>Headache</td><td>0</td><td>2</td></tr>
<tr><td>After treatment</td><td></td><td></td></tr>
<tr><td>Amyostasia (difficulty in standing due to muscular tremor or incoordination)</td><td>1</td><td>1</td></tr>
<tr><td>Testiness (irritation/impatient)</td><td>1</td><td>1</td></tr>
<tr><td>Vigorous dreams</td><td>1</td><td>0</td></tr>
<tr><td>Phonophobia</td><td>1</td><td>0</td></tr>
</table>
</td>
<td>Follow-up:
• 5 patients lost to follow-up (2 did not complete diaries, 2 dropped out [1 in each group] as procedure was unpleasant after 2 sessions, 1 quit with no reason).

Study design issues:
• Sham-controlled blinded study
• Investigators were not blinded.

Population issues
• Patients with migraine prophylactic treatment, cardiac or cerebral pacemaker, metal in the cranium, epilepsy, pregnancy, severe psychiatric or neurological diseases such as Parkinson’s, depression, schizophrenia or complex migraine forms were excluded from study.</td>
</tr>
</table>

Abbreviations used: ICHD, International Classification of Headache Disorders; IHS, International Headache Society; ITT, intention to treat; PDA, personal digital assistant; TMS, single-pulse transcranial magnetic stimulation;

Study details	Key efficacy findings	Key safety findings	Comments
Brighina F (2004)[4] **Randomised controlled trial** Italy (single centre) Recruitment period: not reported Study population: patients with chronic migraine n=**11 (rTMS 6 vs sham 5)** Age: mean 47 years Sex: 64% (7/4) female Patient selection criteria: patients with chronic migraine according to IHS criteria, daily severe headache in last 3 months, on prophylactic treatment by at least 2 months, failed to respond to 3 or more preventive medications and ineffective treatments for drug overuse. Technique: high frequency rTMS over left dorsolateral prefrontal cortex (DLPFC) performed by a tabletop Cadwell stimulator with a water-cooled figure 8 coil at 20Hz and 90% motor threshold intensity for 2 seconds with an interval of 30 seconds, a total of 10 trains on alternative days for12 sessions. Sham rTMS performed with the coil perpendicular to the brain surface and same time schedule. **Follow-up: 2 months** Conflict of interest/source of funding: not reported	Number of patients analysed: **11 (rTMS 6 vs sham 5)** Patients treated by rTMS (n=6) showed a significant reduction of the outcome measures (attack frequency, headache index and medication use) during and 1 month after rTMS treatment as compared with baseline ($p<0.0005$). No significant differences in the outcome measures were observed during and 1 month after treatment. No significant differences in the outcome measures were observed in the sham group (n=5) even through a slight decrease in frequency of attacks (29%), headache index (18%) and number of pills (17%) were observed 1 month after treatment.	Patients tolerated rTMS well and did not complain of side effects.	**Study issues** • Very small sample size • At baseline patients were asked to record headache frequency, pain intensity and number of abortive medications • After 1 month they were re-examined and randomly assigned to rTMS and sham groups. • Patients and investigators were blinded to treatment type. • Baseline mean values for outcome measures did not significantly differ between the rTMS and sham groups. **Population issues** • Patients who reported a score higher than 7 for depression (on Hamilton scale) were excluded.

Abbreviations used: ICHD, International Classification of Headache Disorders; IHS, International Headache Society; ITT, intention to treat; PDA, personal digital assistant; TMS, single-pulse transcranial magnetic stimulation;

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Misra UK (2012)[5]
Case series
India (single centre)
Recruitment period: not reported
Study population: medically resistant migraine patients
n=51
Age: median 32 years
Sex: 88% (45/51) female
Median headache frequency: 3.75 attacks/week; migraine duration: 8 years; headache duration: 1.5 days; number of rescue medication; 3.25/week
Patient selection criteria: aged 15 and over, no response to at least 2 prophylactic drugs for at least 3 months, > 7 attacks per month, diagnosed based on IHS criteria.
Technique: rTMS was performed using magnetic stimulator (Magstim Rapid UK) with an air cooled figure 8 coil of 7cm diameter over the left frontal cortex. Each session had 584 pulses in 412 seconds, given in 10 trains of 8 Hz with an interval of 45 seconds. 3 sessions were given on alternative days. Patients maintained a headache diary for recording results during treatment and follow-up periods.
Follow-up: 1 month
Conflict of interest/source of funding: not reported</td>
<td>Number of patients analysed: 51
50% reduction in headache frequency and/or in VAS score
98% (50/51) patients had more than 50% reduction of headache frequency at the end of 1 week after rTMS and the improvement persisted till the 4th week in 80.4% (41/51) patients.
Improvement in VAS score (measured on a scale 0-100)
The VAS score improved to 81±13.7 in the rTMS week, peaked in the first week (84.7±11.2) and declined in 4th week (67.7 ±18.1).
rTMS on various migraine parameters
<table>
<tr><th>Parameters</th><th>Baseline (mean± SD)</th><th>rTMS week (mean± SD)</th><th>First week (mean± SD)</th><th>Second week (mean± SD)</th><th>Third week (mean± SD)</th><th>Fourth week (mean± SD)</th></tr>
<tr><td>Frequency of headache</td><td>4.5± 2.3</td><td>0.9± 0.8</td><td>0.1± 0.4</td><td>0.9± 1.8</td><td>1.7± 2.2</td><td>2.4 ±2.2
p<0.0001</td></tr>
<tr><td>Severity of headache*</td><td>3.0± 0.2</td><td>0.8± 0.7</td><td>0.2± 0.4</td><td>0.4± 0.6</td><td>0.9± 0.7</td><td>1.4± 0.8
p<0.0001</td></tr>
<tr><td>Functional disability**</td><td>3.4± 0.6</td><td>0.6± 0.6</td><td>0.0 ±0.2</td><td>0.2± 0.5</td><td>0.6± 0.8</td><td>1.18± 0.7
p<0.0001</td></tr>
<tr><td>Rescue analgesic</td><td>4.1± 2.9</td><td>0.6± 0.8</td><td>0.1± 0.4</td><td>0.8 ±1.7</td><td>1.5± 2.0</td><td>2.5± 2.3
p<0.0001</td></tr>
</table>
*graded on a scale 0-3, higher score indicating severe headache as per Piovesan and Silberstien. ** graded on a scale 0-4, higher score indicating inability to perform daily activities requiring bed rest.</td>
<td>There were no serious side effects in any patients during or after rTMS.
Discomfort during rTMS (assessed using a 0-5 face pain scale) in first session was 2.42±0.74 which declined to 1.81±0.70 in the second and 1.37 ± 0.68 in the third session.
Aggravation of headache during stimulation was reported in 3 patients (subsided spontaneously without any medications)
Transient rhinorrhoea in second stimulation session was reported in 1 patient.</td>
<td>Follow-up issues:
• Complete follow-up

Patient issues
• Only 1 patient had visual aura.
• 47% (24/51) patients had a family history of migraine.
• The common migraine triggers were mental and physical stress in 49 and sleep deprivation in 48 patients.
• All patients had photophobia, phonophobia, nausea, vomiting and giddiness symptoms.
• Most patients were resistant to prophylactic medications for a median duration of 12 months.
• 96% (49/51) patients had severe migraine attacks.
• Patients did not receive any prophylactic medications during or after the study and were only given rescue analgesics.
• Patients who were pregnant or had liver or kidney diseases, malignancy, severe hypertension, pacemaker or metallic implants, history of seizure or structural brain lesions were excluded.</td>
</tr>
</table>

Efficacy

Pain-free response for the first treated attack

A multicentre randomised controlled trial (RCT) of 164 patients treated for at least 1 attack of migraine with aura with a handheld sTMS device (n=82) or with sham stimulation (n=82) (modified intention to treat analysis set) reported that pain-free rates 2 hours after stimulation were significantly better with sTMS (39% [32/82]) than with sham stimulation (22% [18/82]; p=0.018). Sustained pain-free response rates (with no recurrence and no rescue drug use) significantly favoured sTMS at 24 hours (29% [24/82] vs 16% [13/82]; p=0.0405) and 48 hours (27% [22/82] vs 13% [11/82]; p=0.0327) after treatment. There were no significant differences in secondary outcomes (headache response at 2 hours, use of rescue drugs, Migraine Disability Assessment [MIDAS] score and consistency of pain relief response) between groups[1].

Improvement in headache

A case series of 42 patients with migraine (including 5 with aura) treated with high-intensity (n=21) or low-intensity stimulation (n=21) double-pulse sTMS (with a tabletop clinic-based device) reported that pain intensity in both groups combined decreased by 75% from baseline values (3.30 vs 2.49, p<0.05). Of those who received 1 treatment (n=42), 69% reported improvement in headache (defined as a decrease in perception of pain of at least 1 level (on a 5-point Likert scale, 5 indicating worst pain) and decrease in the number of headaches occurring after TMS, with 32% reporting no further headache at 24 hours. In individuals with an aura (n=10), relief was reported as 100% and immediate[2].

A case series of 51 patients with ‘medically resistant migraine’ using rTMS for prevention reported that 98% (50/51) of patients had a greater than 50% reduction in headache frequency at the end of 1 week and the improvement persisted until the fourth week in 80.4% (41/51) of patients. Headache frequency and severity, functional disability and rescue drugs were significantly reduced at all time points (1, 2, 3 and 4 weeks, p<0.0001) but the maximum benefit was observed in the first 2 weeks[5].

Reduction of migraine attacks, days, hours, pain intensity and use of analgesics

A RCT of 11 patients comparing rTMS (n=6) against sham treatment (n=5) showed a significant reduction in the outcome measures (attack frequency, headache index and medication use) during and 1 month after rTMS treatment compared with baseline (p<0.0005). No significant differences in the outcome measures were observed in the sham group[4].

A case series of 27 patients with migraine comparing low-frequency rTMS (n=14) against sham stimulation (n=13) for prevention reported no significant differences

between groups for all reported outcomes (including number and duration of migraine attacks, mean pain intensity and use of analgesics). The 'within-group' findings from this study showed a significant decrease in the number of migraine attacks during 8 weeks within the rTMS group from 9.36±2.82 attacks to 6.79±4.28 attacks (p=0.007), and a non-significant decrease within the sham group (numbers not reported; p=0.216). There was a significant reduction in migraine days during 8 weeks in both rTMS and sham groups (from 17.69±11.63 days to 13.15±9.27 days [p=0.012] and from 14.36±5.07 days to 9.50±6.80 days [p=0.006] respectively). The rTMS group showed a significant reduction in migraine hours during 8 weeks from 125.93±80.31 hours to 85.36±72.27 hours, p=0.035; the difference was not significant in the sham group (numbers not reported; p=0.080)[3].

Mean pain intensity changed from 6.26±1.33 to 6.11±1.26 (p=0.455) in the rTMS group; and from 5.52±1.72 to 5.17±2.51 (p=0.839) in the sham group. Differences between the rTMS and sham groups were not significant (p=0.942). The intake of analgesics changed from 14.21±10.13 pills to 12.50±14.65 pills (p=0.232) in the rTMS group; and from 15.15±11.24 pills to 11.81±9.89 pills (p=0.094) in the sham group. Differences between the rTMS and sham groups were not significant (p=0.577)[3].

Safety

No device-related serious adverse events were reported in the RCT of 164 patients. The incidence of adverse events was similar between the sTMS group (14%, 14/102) and sham group (9%, 9/99) within 48 hours after treatment. All events (headache, migraine, sinusitis and paraesthesia) were mild or moderate with the exception of severe nausea (n=1 in each group), severe migraine (n=1, sTMS group) and severe headache (n=1, sTMS group)[1].

Slight 'unsustained' dizziness (n=1) drowsiness (n=1) and tiredness (n=2) were reported in the case series of 42 patients after treatment with low- or high-intensity TMS. None of these events recurred or needed medical attention[2].

Sleepiness (n=1 in each group), uncomfortable or long-lasting sitting (n=1 in each group), headache (n=2 in sham group) and uncomfortable assessment of visual motor threshold (n=5 in rTMS group; n=4 in sham group) were reported during treatment in the case series of 27 patients. Amyostasia (muscle tremor causing difficulty in standing), irritability (n=1 in each group), 'vigorous dreams' and phonophobia (n=1 each in rTMS group) were reported after rTMS treatment in this study[3].

Discomfort (assessed using a 0–5 face pain scale where higher scores indicate greater pain) was 2.42±0.74 during the first session of rTMS, 1.81±0.70 in the second session and 1.37±0.68 in the third session in the study of 51 patients. In the same study, aggravation of headache during stimulation was reported in 3 patients, and transient rhinorrhoea in the second stimulation session was

reported in 1 patient. All these events subsided spontaneously without any medication[5].

Validity and generalisability of the studies

- There is evidence on sTMS for acute treatment of migraine with aura from 1 study.
- There is evidence (from 3 studies) on rTMS as a preventive treatment for migraine – some patients had migraine with aura.
- Stimulation parameters varied across studies in frequency, intensity, duration and interval times.
- Location of stimulation delivery also varied across studies.
- There is lack of long-term data about the efficacy and safety of TMS.

Existing assessments of this procedure

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

Related NICE guidance

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

Interventional procedures

- Percutaneous closure of patent foramen ovale for recurrent migraine. NICE interventional procedure guidance 370 (2010). Available from www.nice.org.uk/guidance/IPG370
- Transcranial magnetic stimulation for severe depression. NICE interventional procedure guidance 242 (2007). Available from www.nice.org.uk/guidance/IPG242

Technology appraisals

- Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. NICE technology appraisal guidance 260 (2012). Available from www.nice.org.uk/guidance/TA260

Clinical guidelines

- Headaches: diagnosis and management of headaches in young people and adults. NICE clinical guideline 150 (2012). Available from www.nice.org.uk/guidance/CG150

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their specialist society or royal college. The advice received is their individual opinion and does not represent the view of the society.

Dr Sam Chong and Manjit Matharu (Association of British Neurologists). Dr Shazia Afridi, Dr Fayyaz Ahmed and Dr Anish Bahra (British Association for the Study of Headache).

- One specialist adviser performs this procedure regularly and the other advisers have never performed the procedure.
- Two specialist advisers considered the procedure to be the first in a new class of procedures. Two other specialist advisers considered the procedure to be novel and of uncertain efficacy and safety. One adviser considered it as a minor variation of an existing procedure because the use of the device is not new.
- Comparators for this procedure include standard abortive treatments (such as simple analgesics, non-steroidal anti-inflammatory drugs and triptans), standard prophylactic drugs (including beta-blockers, anti-epileptics and tricyclic antidepressants) and other procedures such as acupuncture, and botulinum toxin type A occipital nerve blocks and stimulations.
- Specialist advisers stated that fewer than 10% of headache specialists are engaged in this area of work. One adviser stated that very few centres (taking part in a manufacturer study) are performing this procedure; one other adviser stated that lack of device availability through the NHS has restricted the number of specialists recommending the device.
- Anecdotal adverse events reported include transient muscle contraction, mild transient numbness on the occipital region for a few seconds, neurological pain at stimulation site and hearing impairment because of the loud noises from some repetitive TMS.
- Theoretical adverse events included lower seizure threshold, local scalp irritation, nausea, worsening of headache or neck pain, mood disorders: dysphoria and depression, cognitive impairment, triggering of epilepsy during

treatment and ‘kindling’ leading to seizures, dizziness, drowsiness and pain. One adviser stated that long-term use of repetitive TMS may theoretically produce permanent neural changes but it was difficult to speculate what the clinical correlate of these theoretical changes might turn out to be.

- Key efficacy outcomes include reduction in the intensity of pain, pain-free response at 2 hours, sustained pain-free response at 24 hours, headache relief or complete resolution of the migraine attack, reduction in headache days, reduction in headache severity and duration, severity of migraine attacks, improvement in associated symptoms, disability (MIDAS, headache impact test-6 [HIT-6]) and quality of life.
- There are uncertainties about the long-term efficacy of the procedure. One adviser stated that patients with aura would not have developed a headache if only tested on 2 occasions in the published RCT. One adviser stated that there is uncertainty because efficacy results are conflicting and all migraine studies have high placebo response rates. One adviser stated that it is still unclear whether single or repetitive stimulation works better and whether the benefit is sustained.
- Specialist advisers stated that device instructions are simple and no formal training is needed to use the device. One adviser stated that minimal training is required and, for repetitive TMS, clinicians (nurses, healthcare technicians) can be shown how to use this. Some devices can be used at home. For others, attendance in hospital is necessary but special facilities are not needed.
- Post-marketing surveillance data in the UK on123 patients have been collected and experiences were presented at the International Headache Society meeting and the European Headache Migraine Trust International Congress in 2012. Responder rates of 70% for headache and 66% for associated symptoms were reported. Experiences of using the device in 3 pregnant women were also reported.
- Three specialist advisers stated that the procedure is likely to be used in a minority of hospitals but at least 10 in the UK. This will suit patients who are

intolerant to oral or injectable abortive treatments or whose migraine is refractory to other forms of treatment. He stated that recommendations for the use of the device (patient selection) should be made by headache specialists and its use monitored by primary care physicians. One adviser stated that TMS will be undertaken in all district hospitals.

- One specialist adviser stated that there is uncertainty as to whether TMS benefits migraine aura itself or migraine without aura. It has only been used in episodic migraine.
- One specialist adviser stated that there is likely to be rapid diffusion of the procedure, as manufacturers are doing considerable marketing to promote the devices. Two advisers stated that diffusion will be slow but it may be widely used if there is evidence for both acute and preventative treatment.
- Two specialist advisers considered the procedure to potentially have a minor impact on the NHS, in terms of patients eligible for treatment (that is, patients referred from secondary to tertiary care) and use of resources. One of these advisers stated that non-invasive neurostimulation is the next milestone in the treatment of migraine and if proven effective will provide a better option in migraine management. Two advisers considered the procedure to have a moderate impact while another adviser stated that it will have a major impact on the NHS because a large number of patients are eligible for treatment.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme sent 50 questionnaires to one NHS Trust for distribution to patients who had the procedure (or their carers). NICE received 14 completed questionnaires.

The Patient Commentators views on the procedure were consistent with the published evidence and the opinions of the specialist advisers. Overall, people were very positive about the procedure, with everyone saying that they would use it again, including those (14% [2/14]) who were unsure whether the procedure had much effect on them. Some side effects were experienced by 29% (4/14),

including nausea, dizziness, ‘teeth feeling funny’ immediately after use and worsened migraine-related blindness.

Issues for consideration by IPAC

- There are limited studies on the use of TMS in patients with migraine.
- sTMS is used for acute treatment of migraine with aura and rTMS as a preventive treatment for migraine. The Committee may wish to amend the title to ‘transcranial magnetic stimulation for the prevention and treatment of migraine’.
- One study for acute treatment used a portable device for self-treatment immediately after the onset of an aura and all other studies in the overview used table top devices.
- There are not enough data on the optimal number of pulses or stimulus parameters.
- There are no direct comparative trials comparing drug treatment to TMS.
- Ongoing studies:
  - NCT01496950: Double-blind Randomized Clinical Trial to Evaluate Safety and Efficacy of Repetitive Transcranial Magnetic Stimulation in the Preventive Treatment of Chronic Migraine (TMS-CHROMIG); study type: randomized clinical trial; estimated enrolment: 20; study location; Brazil; estimated completion date: 2012; primary outcome: number of days with pain per month. This study is currently recruiting participants.

References

1. Lipton RB, Dodick DW, Silberstein SD et al.(2010) Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomized, double-blind, parallel-group, sham-controlled trial. Lancet Neurol 9(4): 373-80.

2. Clarke BM, Upton AR, Kamath MV et al. (2006) Transcranial magnetic stimulation for migraine: clinical effects. Journal of Headache & Pain 7 (5): 341-46

3. Teepker M, Hotzel J, Timmesfeld N et al. (2010) Low-frequency rTMS of the vertex in the prophylactic treatment of migraine. Cephalalgia 30 (2): 137-44

4. Brighina F, Piazza A, Vitello G et al. (2004) rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. Journal of the Neurological Sciences 227: 67-71

5. Misra UK, Kalita J, Bhoi SK (2012) High frequency repetitive transcranial magnetic stimulation (rTMS) is effective in migraine prophylaxis: an open labelled study. Neurological Research 34 (6): 547-51

Appendix A: Additional papers on transcranial magnetic stimulation for treating and preventing migraine

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

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Almaraz AC, Dilli E, and Dodick DW. (2010) The effect of prophylactic medications on TMS for migraine aura. Headache 50 (10): 1630-33.	n=201 Randomised controlled trial patients with moderate or severe migraine with aura Single-pulse TMS Follow-up:48 hours	Prophylactic medications were used by 41.5% [34/82] in sTMS and 37% [31/82] in sham group. Patients with PM were more likely to report their pain as severe (60 vs 45.5%) than patients not on PM. Sham patients without prophylactic medication (PM) had significantly higher pain-free rate [PFR] than sham patients with PM (P=0.014). There was no difference in PFR between sTMS treated patients with or without PM (P=.5513). Patients treated by sTMS with PM had significantly higher PFR than sham with PM (p=.002). There was no difference in PFR between patients treated by sTMS without PM and sham without PM (p=.4061).	Subgroup analysis of Lipton (2010) study. Assess effect of migraine prophylactic medication use.
Brigo F, Storti M, Nardone R et al. (2012) Transcranial magnetic stimulation of visual cortex in migraine patients: a systematic review with meta-analysis. [Review]. Journal of Headache & Pain 13 (5): 339-49.	Systematic review with meta-analysis (10 trials (277 migraine patients and 193 controls) Adult migraine patients Intervention: TMS	Patients with MA had significant lower PT compared with controls when a circular coil was used (MD -28.33; 95% CI -36.09 to -20.58); a similar result was found in MwA patients (MD -17.12; 95% CI -23.81 to -10.43); using a figure-of-eight coil. There was a significantly higher phosphene in MA patients compared with control subjects (OR 4.21; 95% CI 1.18-15.01). No significant differences were found either in phosphene reporting between patients with MwA and controls, or in PT values obtained with a figure-of-eight coil in MA and MwA patients versus controls. These results support the hypothesis of a primary visual cortex hyper-excitability in MA, providing not enough evidence for MwA.	Systematic review on phosphenes and phosphene threshold by STMS. (not clinical outcomes)
Diener HC. (2010) Single-pulse transcranial magnetic stimulation: a new way to treat migraine attacks with aura. Lancet Neurology 9 (4) 335-337			Review
Dodick D. W, Schembri C. T, Helmuth M et al. (2010) Transcranial magnetic stimulation for migraine: a safety review. Headache 50:1153-63.	TMS adverse events reviewed	Two decades of clinical experience with sTMS have shown it to be a low risk technique in the diagnosis, monitoring, and treatment of neurological and psychiatric disease in adults. Subjects have undergone TMS for diagnostic,	Review

		investigative, and therapeutic intervention trial purposes with minimal adverse events or side effects. No discernible evidence exists to suggest that sTMS causes harm to humans. No changes in neurophysiological function have been reported with sTMS use.	
Fumal A, Bohotin V, Vandenheede M et al. (2003) Transcranial magnetic stimulation in migraine: a review of facts and controversies. Acta Neurologica Belgica 103 (3) 144-54.			Review of TMS and rTMS over motor or visual cortices in patients with migraine.
Kaniecki RG, Taylor FR, and Landy SH. (2010) Abstracts and citations. [Commentary on] Lipton RB, Dodick DW, Silberstein SD, et al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. Lancet Neurol. 2010;9:373-380. Headache: The Journal of Head & Face Pain 50 (8): 1390-92.			Commentary on Lipton 2010
Lipton RB and Pearlman SH. (2010) Transcranial magnetic simulation in the treatment of migraine. [Review] [60 refs]. Neurotherapeutics 7 (2) 204-212.		A small body of evidence suggests that rTMS may have a role, but further studies are needed. In this review, data on TMS as a treatment of migraine is summarised, and directions for future research suggested.	Review
Lo YL. (2010) Headache: migraine, magnetic stimulation and cortical excitability. Nature Reviews Neurology 6 (8): 425-7.			Review about Lipton 2010 and role of cortical excitability.

Milnik V, Waibler D, and Kienle M (2013). Repetitive transcranial magnetic stimulation in acute treatment of migraine with or without aura. Neurophysiologie-Labor 35 (1) 41-46.		Migraine is a common disorder that can cause significant impairment and loss of quality of life. Acute migraine attacks can be treated with transcranial magnetic stimulation. This paper reports on the use of transcranial magnetic stimulation (TMS) to treat migraine with and without aura and intervals of pain. The results of this study provided two insights: they show that TMS is an effective, pain relief in patients during migraine attacks and as an effective preventive measure.	Non English article
Mohammad Y. M, Hughes G, Nkrumah M et al. Self-administered transcranial magnetic stimulation (TMS), during aura phase, improves and aborts migraine headache. 48th Annual Scientific Meeting of the American Headache Society. June 2006. Abstract F42.			Conference abstract
Mohammad YM, Kothari R, Hughes G et al. (2006) Transcranial magnetic stimulation (TMS) relieves migraine headache. Headache 46: 839.	RCT n=42 (23 TMS and 19 placebo) Adult migraine patients with aura	69% TMS headaches reported to have no or mild pain 2 hours post treatment compared to 48% in placebo group. (p=0.10).There were no side effects reported in either group.	Conference abstract
Misra UK, Kalita J et al. (2012) Repetitive transcranial magnetic stimulation (RTMS) results in elevation of b endorphin level and relief of migraine headache. Annals of Neurology 72 S89	Comparative study n=25rTMS (25 matched controls) Migraine patients>4 attacks Repetitive transcranial magnetic stimulation Follow-up: 7 days	Baseline plasma B endorphin (BE) levels were lower in migraine compared to controls. Migraine frequency, duration, severity, functional disability, and analgesic use significantly reduced on 7th day compared to baseline. After rTMS BE levels significantly increased (6.58+/-3.33ng/ml) compared to baseline (4.35+/-2.29ng/ ml P = 0.001) and the change in BE correlated with clinical improvement.	Abstract only.
Ray K. Migraine: Portable sTMS device relieves the pain of migraine. Nature Reviews Neurology 6 (5) 239-2010.			Article with some research highlights about Lipton 2010.
Starling A. J, Scottsdale A. Z, Dodick R. P et al. Comparison of effect size between active and placebo single pulse transcranial magnetic stimulation (spTMS)	Comparisons from existing drug and sTMS placebo-controlled	For mild migraine, the proportion of patients that was headache-free 2 hours after treatment in the sTMS trial was 39.4%. In the drug trials, where a number of triptans at various therapeutic doses were tested, the proportions of patients headache-free two hours after treatment	Conference abstract No information in the abstract about patient

versus triptans for the acute treatment of migraine. American Academy of Neurology Meeting. April 2011. Abstract P05.271.	trials Systematic review	were between 36.4 and 67.4%. For moderate to severe migraine, the proportion of patients that was headache-free 2 hours after treatment was 35% in the sTMS trial and between 35 and 37.5% in the drug trials.	groups in each trial, including the presence of aura.
Weatherall Mw, Bhola, Giffin N, and Goadsby Pj. (2013). Post market pilot programme with single pulse transcranial magnetic stimulation (sTMS) for acute treatment of migraine: SpringTMSâ„¢ use in migraine. Journal of Headache & Pain 14 1-2.		Study design = Case series n= 37 Follow up= 3 months Study population-patients with acute migraine Technique= single pulse sTMS RESULTS: Sixty-one patients have been prescribed sTMS from which 37 (61%) have been using the device for a minimum of three months and completed surveys. A reduction or alleviation of pain was reported by 73%. Associated symptoms were improved in 63% of patients or for some, did not develop. A reduction in the number of headache days was reported by 53%. When using the combination of sTMS and a medicine, 30% reported no headache recurrence. Quality of sleep improved in 17%. The treatment was well tolerated with no adverse events reported. Conclusion: The sTMS device is a new and effective acute migraine treatment. This CE marked device is safe to use in clinical practice and has reliable, reproducible effects on migraine over time.	Poster presentation. No safety events reported.
Zierhut KC, Richter MM, Renner, TJ et al. (2007) Occurrence of reversible bilateral scotoma 1 hour after single-pulse transcranial magnetic stimulation: A case report [3]. Journal of Clinical Psychiatry 68 (3): 488-89	Case report n=1 30 year healthy man TMS and multichannel near-infrared spectroscopy (NIRS)	Patient developed a reversible bilateral flicker scotoma 1 hour after TMS over the motor area of the right abductor pollicis brevis muscle. The symptoms abated completely after 4 hours.	Healthy patient with no history of seizures or migraine.

Appendix B: Related NICE guidance for transcranial magnetic stimulation for treating and preventing migraine

Guidance	Recommendations
Interventional procedures	**Percutaneous closure of patent foramen ovale for recurrent migraine. NICE interventional procedure guidance 370 (2010)** 1.1 Current evidence on the efficacy of percutaneous closure of patent foramen ovale (PFO) for recurrent migraine is inadequate in quality and quantity. The evidence on safety shows a small incidence of well-recognised but sometimes serious adverse events, including device embolisation and device prolapse (each reported in less than 1% of patients). Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research. 1.2 Clinicians wishing to undertake percutaneous closure of PFO for recurrent migraine should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and their carers understand the uncertainty about the procedure's efficacy and the possibility of serious complications. Clinicians should provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. 1.3 Patient selection for percutaneous closure of PFO for recurrent migraine should be carried out by a neurologist or other specialist in headache followed by an interventional cardiologist. Use of this procedure should be restricted to patients who are severely affected by recurrent, refractory migraine. 1.4 The procedure should be done by an interventional cardiologist and supporting team with specific training in the procedure. 1.5 The procedure should only be carried out in units where there are arrangements for emergency cardiac surgical support in the event of complications. 1.6 Data on all patients having this procedure should be submitted to the UK Central Cardiac Audit Database. 1.7 NICE encourages further research into this procedure, which should investigate the uncertainty surrounding the

	aetiology and natural history of migraine in patients with PFO. NICE may review this procedure on publication of further evidence. **Transcranial magnetic stimulation for severe depression. NICE interventional procedure guidance 242 (2007)** 1.1 Current evidence suggests that there are no major safety concerns associated with transcranial magnetic stimulation (TMS) for severe depression. There is uncertainty about the procedure's clinical efficacy, which may depend on higher intensity, greater frequency, bilateral application and/or longer treatment durations than have appeared in the evidence to date. TMS should therefore be performed only in research studies designed to investigate these factors. 1.2 Future research should aim to address patient selection criteria, the optimal use of this procedure in relation to other treatments, and the duration of any treatment effect. Clinicians should collaborate to ensure that studies are sufficiently large to be adequately powered. The Institute may review the procedure upon publication of further evidence.
Technology appraisals	**Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. NICE technology appraisal guidance 260 (2012)** 1.1 Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with chronic migraine (defined as headaches on at least 15 days per month of which at least 8 days are with migraine): • that has not responded to at least three prior pharmacological prophylaxis therapies **and** • whose condition is appropriately managed for medication overuse. 1.2 Treatment with botulinum toxin type A that is recommended according to 1.1 should be stopped in people whose condition: • is not adequately responding to treatment (defined as less than a 30% reduction in headache days per month after two treatment cycles) **or** • has changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months. 1.3 People currently receiving botulinum toxin type A that is not recommended according to 1.1 and 1.2 should have the option to continue treatment until they and their clinician consider it appropriate to stop

Clinical guidelines	**Headaches: diagnosis and management of headaches in young people and adults. NICE clinical guideline 150 (2012)** **Migraine with aura (Diagnosis)** 1.2.2 Suspect aura in people who present with or without headache and with neurological symptoms that: • are fully reversible **and** • develop gradually, either alone or in succession, over at least 5 minutes **and** • last for 5–60 minutes. 1.2.3 Diagnose migraine with aura in people who present with or without headache and with one or more of the following typical aura symptoms that meet the criteria in recommendation 1.2.2: • visual symptoms that may be positive (for example, flickering lights, spots or lines) and/or negative (for example, partial loss of vision) • sensory symptoms that may be positive (for example, pins and needles) and/or negative (for example, numbness) • speech disturbance. 1.2.4 Consider further investigations and/or referral for people who present with or without migraine headache and with any of the following atypical aura symptoms that meet the criteria in recommendation 1.2.2: • motor weakness **or** • double vision **or** • visual symptoms affecting only one eye **or** • poor balance **or** • decreased level of consciousness. **Migraine with or without aura (Management)** **Acute treatment** 1.3.10 Offer combination therapy with an oral triptan[8] and an NSAID, or an oral triptan[8] and paracetamol, for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. For young people aged 12–17 years consider a nasal triptan in preference to an oral triptan[8]. 1.3.11 For people who prefer to take only one drug, consider monotherapy with an oral triptan[8], NSAID, aspirin[7] (900 mg) or paracetamol for the acute treatment of migraine, taking into account the person's preference, comorbidities and risk of adverse events. 1.3.12 When prescribing a triptan[8] start with the one that has the lowest acquisition cost; if this is consistently ineffective, try one or more alternative triptans.

	1.3.13 Consider an anti-emetic in addition to other acute treatment for migraine even in the absence of nausea and vomiting. 1.3.14 Do not offer ergots or opioids for the acute treatment of migraine. 1.3.15 For people in whom oral preparations (or nasal preparations in young people aged 12–17 years) for the acute treatment of migraine are ineffective or not tolerated: • offer a non-oral preparation of metoclopramide or prochlorperazine[9] and • consider adding a non-oral NSAID or triptan[8] if these have not been tried. Prophylactic treatment 1.3.16 Discuss the benefits and risks of prophylactic treatment for migraine with the person, taking into account the person's preference, comorbidities, risk of adverse events and the impact of the headache on their quality of life. 1.3.17 Offer topiramate[10] or propranolol for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. Advise women and girls of childbearing potential that topiramate is associated with a risk of fetal malformations and can impair the effectiveness of hormonal contraceptives. Ensure they are offered suitable contraception. 1.3.18 If both topiramate[10] and propranolol are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over 5–8 weeks or gabapentin[11] (up to 1200 mg per day) according to the person's preference, comorbidities and risk of adverse events. 1.3.19 For people who are already having treatment with another form of prophylaxis such as amitriptyline[12], and whose migraine is well controlled, continue the current treatment as required. 1.3.20 Review the need for continuing migraine prophylaxis 6 months after the start of prophylactic treatment. 1.3.21 Advise people with migraine that riboflavin (400 mg[13] once a day) may be effective in reducing migraine frequency and intensity for some people. <u>Treatment of migraine during pregnancy</u> 1.3.24 Offer pregnant women paracetamol for the acute treatment of migraine. Consider the use of a triptan[8] or an NSAID after discussing the woman's need for treatment and the risks associated with the use of each medication during pregnancy. 1.3.25 Seek specialist advice if prophylactic treatment for migraine is needed during pregnancy.

Appendix C: Literature search for transcranial magnetic stimulation for treating and preventing migraine

Databases	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	22/10/2013	Issue 10 of 12, October 2013	0
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	22/10/2013	Issue 3 of 4, July 2013	1
HTA database (Cochrane Library)	22/10/2013	Issue 3 of 4, July 2013	1
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	22/10/2013	Issue 9 of 12, September 2013	12
MEDLINE (Ovid)	22/10/2013	1946 to October Week 1 2013	1
MEDLINE In-Process (Ovid)	22/10/2013	October 21, 2013	3
EMBASE (Ovid)	22/10/2013	1974 to 2013 Week 42	14
CINAHL (NLH Search 2.0)	22/10/2013	1981 to present	37
PubMed	22/10/2013	n/a	2
JournalTOCS	22/10/2013	n/a	2

Trial sources searched on

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched
- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- Evidence Updates (NHS Evidence)

General internet search

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

MEDLINE search strategy

1	Migraine Disorders/
2	Migraine with Aura/
3	(migraine* adj2 with adj3 aura*).tw.
4	(acute* adj3 migrain*).tw.
5	(migrainous* adj3 headache*).tw.
6	((classic* or basilar* or hemipleg* or complicated*) adj3 migraine*).tw.
7	or/1-6
8	Transcranial Magnetic Stimulation/
9	((transcranial or trans-cranial) adj3 magnetic adj3 (stimulat* or activat*)).tw.
10	(single adj3 pulse adj3 magnet* adj3 stimul*).tw.
11	(repetit* adj3 pulse adj3 magnet* adj3 stimul*).tw.
12	TMS.tw.
13	sTMS.tw.
14	rTMS.tw.
15	SpringTMS.tw.
16	or/8-15
17	7 and 16
18	animals/ not humans/
19	17 not 18