NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcranial magnetic stimulation for obsessive-compulsive disorder

Obsessive-compulsive disorder is a mental health condition in which a person has obsessive thoughts (repeated, unwanted and unpleasant thoughts, images or urges). The person feels the need to carry out compulsive (repetitive) behaviours to try to relieve the unpleasant feelings brought on by the obsessive thoughts. In this procedure, a device containing an electromagnet is placed against the scalp. The device produces pulses of electromagnetic energy that stimulate specific areas in the brain through the skull (transcranial). Treatment is a daily session of about 30 minutes, for a few weeks. The aim is to reduce the obsessive-compulsive thoughts and behaviours.

Contents

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Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure 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 September 2019.

Procedure name

- Transcranial magnetic stimulation for obsessive-compulsive disorder.

Professional societies

- Royal College of Psychiatrists
- The British Psychological Society.

Description of the procedure

Indications and current treatment

Obsessive-compulsive disorder (OCD) is a mental health condition in which a person has obsessive thoughts (repeated, unwanted and unpleasant thoughts, images or urges). The person feels compelled to carry out compulsive (repetitive) behaviours to try to relieve the unpleasant feelings brought on by the obsessive thoughts.

NICE's guideline on obsessive-compulsive disorder and body dysmorphic disorder describes the treatment of OCD. Treatment options include psychological interventions and drug treatment (typically selective serotonin reuptake inhibitors [SSRIs]).

What the procedure involves

Transcranial magnetic stimulation (TMS) is done with the patient awake and sitting in a comfortable chair. The operator places an electromagnetic coil over a specific region of the head. The coil delivers electromagnetic pulses through the

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skull that stimulate neurons (brain cells) by inducing small electrical currents within the brain. Different areas of the brain may be targeted, and a variety of stimulation protocols may be used. Treatment with TMS usually comprises daily sessions lasting about 30 minutes, for a few weeks. The aim is to reduce the symptoms of OCD.

In repetitive TMS (rTMS), repetitive pulses of electromagnetic energy are delivered at various frequencies (low or high) or stimulus intensities. The intensity of stimulation is usually titrated against the minimum intensity needed to elicit a motor response when stimulating the motor cortex, known as the motor threshold. Determining the motor threshold for rTMS can be done visually (such as by observing targeted hand muscle movements) or by using electromyography.

Conventional rTMS is repeated individual pulses at a pre-set interval (train of pulses), and theta-burst rTMS is repeated short bursts of pulses at a pre-set interval (train of bursts). Deep TMS stimulates deeper and broader brain regions compared with conventional rTMS.

Outcome measures

The **Yale-Brown Obsessive Compulsive Scale (Y-BOCS)** is designed to rate the severity and type of symptoms in patients with OCD. It consists of 10 questions, 5 on obsessive thoughts and 5 on compulsive behaviour. Each item is rated from 0 (no symptoms) to 4 (extreme symptoms) with a total range from 0 to 40.

The **Clinical Global Impression (CGI)** rating scales are measures of symptom severity, treatment response and the efficacy of treatments in treatment studies of patients with mental disorders.

- The **Clinical Global Impression - Improvement scale (CGI-I)** is a 7-point scale for which the clinician needs to assess the changes in the condition compared with the baseline, with ‘1’ being very much improved and ‘7’ being very much worse.

- The **Clinical Global Impression – Severity scale (CGI-S)** is a 7-point scale for which the clinician needs to rate the severity of the patient’s condition at the time of assessment, with ‘1’ being normal, not at all ill and ‘7’ being the most extremely ill.

The **Hamilton Depression Rating Scale (HAM-D)** is a multi-item clinician-administered depression assessment scale in which a lower score indicates normal mood and a higher score shows severity of the condition.

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The **Hamilton Anxiety Rating Scale (HAM-A)** is used to measure the severity of anxiety symptoms. This clinician-administered scale consists of 14 items and each item is score ranged from 0 (not present) to 4 (severe), with a total score range of 0–56, where less than 17 indicates mild severity, 18 to 24 mild to moderate severity and 25 to 30 moderate to severe.

Efficacy summary

Reduction in symptoms

Yale-Brown Obsessive Compulsive Scale

In a meta-analysis of 18 randomised controlled trials (RCTs) including 484 patients who had active or sham low- or high-frequency rTMS, active rTMS was statistically significantly superior to sham rTMS in reducing the Y-BOCS score (g=0.79, 95% confidence interval [CI] 0.43 to 1.15, p<0.001; I^2=71%, p<0.001).[1]

In an RCT of 99 patients who had active or sham high-frequency deep TMS, the Y-BOCS score decreased by 6.5 (95% CI 4.3 to 8.7) and 4.1 (95% CI 1.9 to 6.2) points respectively at 4-week follow up (p=0.03). The rate of full response was 45% (19/42) in the active deep TMS group and 18% (8/45) in the sham group at 4-week follow up (p=0.006).[2]

In an RCT of 41 patients who had high-frequency, low-frequency or sham deep TMS, the response rates (30% or greater reduction in Y-BOCS score relative to baseline) were 44% (7/16) in the high-frequency deep TMS group and 7% (1/14) in the sham group at the end of treatment (p<0.05). At 1-month follow up, the response rate was 44% (4/9) in the high-frequency deep TMS group and 0% (0/9) in the sham group (p<0.05).The low-frequency group was excluded from the final analysis because of a lack of consistent response and limited rate of recruitment. The proportion of patients with a 35% reduction or more in Y-BOCS at the end of 5 weeks of treatment was 29% (5/16) in the high-frequency group and 7% (1/14) in the sham group (p=not significant).[3]

In a case series of 79 patients who had low-frequency rTMS, the mean Y-BOCS score improved from 28.5 at baseline to 20.8 at the end of treatment (p<0.001). The proportion of patients with a partial response (reduction in score of 25% or more) was 57% (45/79) and a complete response (reduction in score of 35% or more) was 41% (32/79). Binary logistic regression analysis suggested that the presence of comorbid depression and higher baseline Y-BOCS scores were associated with a lower rate of response to rTMS.[4]

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In an RCT of 40 patients who had active or sham low-frequency rTMS, the percentage reduction in Y-BOCS scores was 24% in the active group and 15% in the sham group (p=0.27). The response rate (35% of more decrease in Y-BOCS score) was 32% (6/19) and 18% (3/17) at the end of treatment (p=0.451).[5]

In an RCT of 57 patients who had active or sham low-frequency rTMS with SSRIs, the mean Y-BOCS scores reduced from 17.2 at baseline to 11.7 at the end of 4 weeks of treatment in the active rTMS group (p<0.01) and from 18.1 to 14.6 in the sham group (p<0.01). The difference in scores between the 2 groups was statistically significant (p<0.05).[6]

In an RCT of 50 patients who had low-frequency rTMS or antipsychotic augmentation, the mean Y-BOCS scores reduced from 30.16 to 20.92 and from 31.44 to 25.56 respectively at the end of treatment. The proportion of 'responders' was 68% (17/25) in the rTMS group compared with 24% (6/25) in the antipsychotics group.[8]

In an RCT of 60 patients who had high-frequency rTMS as add-on treatment, high-frequency rTMS as monotherapy or sham rTMS (also included in the meta-analysis), a good response was reported for 55% (11/20), 25% (5/20) and 5% (1/20) respectively (p=0.07 between sham and monotherapy; p=0.05 between monotherapy and add-on treatment; p=0.006 between sham and add-on treatment). The mean Y-BOCS scores reduced from 25.9 to 20.6 in the add-on group (p=0.001), from 22.7 to 20.8 in the monotherapy group (p=0.16) and from 23.0 to 21.7 in the sham group (p=0.23).[7]

Clinical Global Impression scale

In the RCT of 99 patients, the proportion of patients who had a 'moderate to very much' clinical improvement as measured on the CGI-I scale at the end of treatment was 49% (20/41) with active high-frequency deep TMS and 21% (9/43) with sham (p=0.011). At the 4-week follow up, the proportions were 49% (19/39) and 28% (11/40) respectively (p=not significant). The proportion of patients classified as 'improved' on the CGI-S scale was 61% (25/41) with active deep TMS and 33% (14/43) with sham at the end of treatment (p=0.022). At the 4-week follow up, the proportions were 64% (25/39) and 45% (18/40) respectively (p=not significant).[2]

In the RCT of 41 patients, the proportion of patients with a score of 2 or less on the CGI-I scale (very much improved or much improved) was 69% (11/16) with active high-frequency deep TMS and 7% with sham (1/14) at the end of treatment (p<0.001). At 1-week follow up, the proportions were 64% (7/11) and 8% (1/13; p<0.01) and at 1-month follow up, they were 56% (5/9) and 33% (3/9) respectively (p<0.35).[3]

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In the RCT of 40 patients, the CGI-S scores reduced from 4.47 at baseline to 3.79 at week 3 with active low-frequency rTMS and from 4.71 to 4.18 with sham (p=not significant between groups).[5]

Motor threshold

In the RCT of 60 patients who had high-frequency rTMS as add-on treatment, high-frequency rTMS as monotherapy or sham rTMS (also included in the meta-analysis), there were statistically significant increases in motor threshold in the active treatment groups but not the sham group. In the add-on group, the motor threshold increased from 63.9 at baseline to 69.5 after treatment (p=0.03), in the monotherapy group it increased from 71.0 to 80.2 (p=0.002) and in the sham group it increased from 71.0 to 71.6 (p=0.8).[7]

Hamilton Depression and Anxiety Rating scales

In the RCT of 40 patients, the HAM-D scores reduced from 8.11 at baseline to 7.53 at week 3 with active low-frequency rTMS and from 8.18 to 6.94 with sham (p=not significant between groups). The HAM-A scores reduced from 6.21 at baseline to 4.21 at week 3 and from 6.47 to 5.18 respectively (p=not significant between groups).[5]

In the RCT of 57 patients who had active or sham low-frequency rTMS with SSRIs, the mean HAM-A scores reduced from 12.8 at baseline to 8.1 at the end of 4 weeks treatment in the active rTMS group (p=not significant) and from 10.1 to 8.6 in the sham group (p=not significant). The mean HAM-D scores reduced from 16.2 at baseline to 8.4 at the end of 4 weeks treatment in the active rTMS group (p<0.01) and from 14.0 to 10.6 in the sham group (p<0.05).[6]

Safety summary

Seizure

Seizure or pseudo-seizure was reported in 2 patients who had OCD (1 of whom also had depression and panic) in a review of 33 patients who had seizures after deep rTMS. The overall rate of seizures after deep rTMS was estimated at less than 0.1%.[9]

Headache

Headache was reported by 38% of patients who had active deep TMS and 35% of patients who had sham deep TMS in the RCT of 99 patients.[2]

Headache was reported by 13% (10/79) of patients who had low-frequency rTMS in the case series of 79 patients.[4]

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Side effects including headache and fatigue were reported by 19% (3/16) of patients who had high-frequency deep TMS and 7% (1/14) of patients who had sham deep TMS in the RCT of 60 patients.[3]

Headache was reported as an adverse event in the RCT of 57 patients (frequency not reported).[6]

Scalp discomfort

Localised scalp discomfort was reported by 17% (13/79) of patients who had low-frequency rTMS in the case series of 79 patients.[4]

Localised scalp pain was reported as an adverse event in the RCT of 57 patients (frequency not reported).[6]

Other

Headache, sedation, concentration difficulties and failing memory were the most commonly reported adverse effects over the course of treatment in the RCT of 40 patients; the prevalence of these adverse effects was not statistically significantly different between the active treatment and sham groups.[5]

Dizziness was reported as an adverse event in the RCT of 57 patients (frequency not reported).[6]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts 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 happened). For this procedure, professional experts listed the following anecdotal adverse events: headache, scalp discomfort, fatigue and dizziness (all transient). They considered that the following were theoretical adverse events: muscle twitching, syncope, cognitive impairment, neck stiffness and increased anxiety because of unfamiliarity.

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The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to TMS for OCD. The following databases were searched, covering the period from their start to 17 July 2019: 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 the literature 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 when no clinical outcomes were reported or when 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 OCD
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 IP overview

This IP overview is based on about 900 patients from 1 systematic review and meta-analysis, 6 RCTs (1 of which is also included in the systematic review), 1 case series and 1 review of seizures reported after deep rTMS.[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 the appendix.

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Table 2 Summary of key efficacy and safety findings on transcranial magnetic stimulation for obsessive-compulsive disorder

Study 1 Rehn S (2018)

Details

Study type	**Systematic review and meta-analysis**
Country	Not reported for the individual studies
Recruitment period	Search date: December 2016
Study population and number	**n=484 (262 active rTMS, 222 sham rTMS); 18 RCTs** Patients with OCD
Age and sex	• Active rTMS: mean 34 years; 57% (143/252) male • Sham rTMS: mean 34 years; 52% (118/225) male
Patient selection criteria	Inclusion criteria: patients aged 18 to 75 years with a primary diagnosis of OCD according to the Diagnostic and Statistical Manual of Mental disorders (DSM-IV or DSM-IV-TR) or the International Classification of Diseases; randomised, sham-controlled trials with either single or double blinding or parallel or crossover design (with only data from the initial randomisation being used for the latter to avoid carryover effects; more than 5 patients randomised per study arm; low frequency (1 Hz or lower) or high frequency (5 Hz or above) for 5 or more sessions either as monotherapy or as an augmentation strategy for OCD; reported pre- and post-rTMS Y-BOCS scores and standard deviation to evaluate the severity of symptoms as the outcome. Studies were excluded if they started rTMS concurrently with a new psychotropic medication or if they otherwise did not meet the inclusion criteria.
Technique	**High- or low-frequency rTMS** The cortical target was the right DLPFC in 5 studies, the left DLPFC in 3 studies, bilateral DLPFC in 3 studies, the pre-SMA in 3 studies, the left OFC in 1 study, the right OFC in 1 study, the SMA in 1 study and a combination of right DLPFC and pre-SMA in 1 study. Low-frequency rTMS was used in 11 studies. The number of sessions ranged from 10 to 30 (mean 14.6). Treatment duration ranged from 1 to 6 weeks. Different strategies were used for the control groups: some used sham coils (n=7) and others used tilted coils (n=10). One study used an unplugged device.
Follow up	**Range 1 to 12 weeks (not reported for 10 studies)**
Conflict of interest/source of funding	None for authors of review

Analysis

Follow-up issues: Data relating to Y-BOCS scores at 4 weeks or less after rTMS were available from 6 RCTs. Data relating to Y-BOCS scores at 12 weeks after rTMS were available from 3 RCTs.

Study design issues: The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Data extraction was done using a standardised data extraction form. Authors were not contacted for missing data. Hedge's g and 95% CIs were calculated for the effectiveness of rTMS in treating OCD using the primary outcome measure of reduction in Y-BOCS score. This was done using a random effects model. Subgroup analyses were done to assess the effect of using different targets and different stimulation frequencies. Egger's regression analysis showed that publication bias was present (p=0.004).

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Study population issues: Many of the enrolled patients had resistant OCD and many patients had maintenance pharmacological treatments throughout the trials. Most of the studies included patients with comorbid anxiety and depression.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **484 (262 versus 222)**

Improvement in Y-BOCS scores

Active rTMS was statistically significantly superior to sham rTMS in reducing the Y-BOCS score (g=0.79, 95% CI 0.43 to 1.15, p<0.001); I^2=71.3%, p<0.001 (authors suggest the heterogeneity was mainly caused by 2 studies).

Subgroup analyses

Subgroups	Number of studies	Heterogeneity I^2 (%)	p for I^2	Hedges' g	95% CI	p for Hedges' g
Cortical target						
SMA	4	91.04	<0.001	1.68	0.07 to 3.29	0.041
Bilateral DLPFC	3	48.67	0.14	1.18	0.45 to 1.91	0.002
Right DLPFC	6	57.19	0.04	0.58	0.20 to 0.97	0.003
Left DLPFC	3	0	0.81	0.24	−0.17 to 0.65	0.253
OFC	2	0	0.72	0.60	−0.02 to 1.22	0.059

Subgroup analyses (continued)

Subgroups	Number of studies	Heterogeneity I^2 (%)	p for I^2	Hedges' g	95% CI	p for Hedges' g
Frequency						
High	7	53.30	0.05	0.55	0.13 to 0.97	0.01
Low	11	77.35	<0.001	0.97	0.42 to 1.51	0.001
Follow up						
<4 weeks	6	84.48	<0.001	0.81	0.01 to 1.60	0.047
12 weeks	3	79.27	0.008	1.26	0.12 to 2.39	0.030

Visualisation of the forest plot suggested that the heterogeneity in the SMA studies was caused by 2 studies. When these were removed, heterogeneity was no longer statistically significant (I^2=0%, p=0.56) and active rTMS was not statistically significantly superior to sham (g=0.22, 95% CI −0.31 to 0.74).

When 3 studies were removed from the low-frequency analysis, heterogeneity was no longer statistically significant (I^2=0%, p=0.79) but there was still a statistically significant improvement with active rTMS compared with sham (g=0.42, 95% 0.14 to 0.70, p=0.003)

The authors noted that the high heterogeneity in the follow-up subgroup analysis was most likely because there was a lack of consistency in the length of follow up in the RCTs.

Safety

No safety data were reported.

Abbreviations used: CI, confidence interval; DLPFC, dorsolateral prefrontal cortex; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; RCT, randomised controlled trial rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; Y-BOCS, Yale-Brown Obsessive Compulsive Scale

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Study 2 Carmi L (2019)

Details

Study type	**Randomised controlled trial**
Country	US (9 sites), Israel (1 site), Canada (1 site)
Recruitment period	2014 to 2017
Study population and number	**n=99 (48 high-frequency deep TMS, 51 sham deep TMS)** Patients with OCD
Age and sex	Modified intention-to-treat sample: • Active deep TMS: mean 41 years; 43% (20/47) male • Sham deep TMS: mean 37 years; 40% (19/47) male
Patient selection criteria	Inclusion criteria: patients with a diagnosis of OCD as a primary disorder confirmed by a certified clinician using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental disorders (DSM-IV), age between 22 and 68 years, having treatment in an outpatient setting, Y-BOCS score of 20 or more. Patients had to be either in maintenance treatment with a therapeutic dose of an SSRI for at least 2 months before randomisation, or in maintenance treatment on cognitive behavioural therapy and symptoms have failed to respond adequately to at least 1 trial of an SSRI. Exclusion criteria included any primary axis I diagnosis other than OCD, severe neurological impairment, and any condition associated with an increased risk of seizures.
Technique	**High-frequency deep TMS** Device: Magstim Rapid2 TMS stimulator (Magstim, UK) equipped with an H-shaped coil design (H7, Brainsway, Israel). The H7 coil was used to stimulate the dorsal medial prefrontal cortex and the anterior cingulate cortex bilaterally. The active treatment group had 20 Hz deep TMS at 100% of resting motor threshold, with 2-second pulse trains and 20-second intertrain intervals, for a total of 50 trains and 2,000 pulses per session. The sham treatment group had treatment with a sham coil using identical technical parameters, which induced scalp sensations but without the electrical field penetrating into the brain. A 3 to 5-minute individualised symptom provocation was done before each treatment to activate the relevant neuronal circuit, with the aim of achieving a self-reported distress score of 4 to 7 out of 10. The patient was asked to keep thinking about the specific obsession during the treatment. The treatment phase lasted 6 weeks, with 5 weeks of daily treatments 5 days a week and 4 treatments during the sixth week (total 29 sessions).
Follow up	**4 weeks**
Conflict of interest/source of funding	The trial was supported by Brainsway Ltd. One author is the chief medical officer of and has a financial interest in Brainsway, and ownership interest in Advanced Mental Health Care Inc. One author is a key inventor of deep TMS and has a financial interest in Brainsway. Several authors have received research, travel or grant support from Brainsway.

Analysis

Follow-up issues: 89% of the active treatment group and 96% of the sham treatment group completed the study. Five patients dropped out of the active treatment group during treatment: 1 had suicidal thoughts, 1 had treatment discomfort and 3 had conflicting schedules. Two patients in the sham group dropped out during treatment, both because of conflicting schedules. An additional patient was enrolled but withdrew consent. The modified intention-to-treat sample included 94 patients (4 patients had changes to their medication and 1 patient had another diagnosis).

Study design issues: Prospective, multicentre double-blind randomised controlled trial. Patients were recruited through web advertisements and referrals from local physicians. Computerised randomisation was used to assign each patient to a treatment group. Patients, operators and raters were blind to treatment allocation. The primary outcome measure was the change in Y-BOCS score from baseline to the end of treatment (6 weeks). Secondary outcome measures included results at 1 month follow up and rate of full response. A full response was defined as a reduction of 30% or more and a

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partial response was a reduction of 20% or more. The change from baseline in Clinical Global Impression scale (Severity) was classified into 3 categories: improved, no change, and worsened.

Study population issues: There were no statistically significant differences between the 2 groups for baseline clinical assessment data. The mean Y-BOCS scores were 27.7 in the active treatment group 26.9 in the sham treatment group. Most patients did not have comorbid depression.

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Key efficacy and safety findings

Efficacy

Number of patients analysed: **94 (47 versus 47)**

Y-BOCS score – decrease from baseline (points)

	Active deep TMS	Sham deep TMS	p
At end of treatment	6.0 (95% CI 4.0 to 8.1)	3.3 (95% CI 1.2 to 5.3)	0.01
4-week follow up	6.5 (95% CI 4.3 to 8.7)	4.1 (95% CI 1.9 to 6.2)	0.03

Rate of full response

	Active deep TMS	Sham deep TMS	p
At end of treatment	38.1% (16/42)	11.1% (5/45)	0.003
4-week follow up	45.2% (19/42)	17.8% (8/45)	0.006

Rate of partial response at 4-week follow up

- Active deep TMS=59.5% (25/42)
- Sham deep TMS=42.2% (19/45), p=0.106

Clinical Global Impression scale – Improvement scale; proportion of patients reporting a 'moderate to very much' clinical improvement

	Active deep TMS	Sham deep TMS	p
At end of treatment	48.8% (20/41)	20.9% (9/43)	0.011
4-week follow up	48.7% (19/39)	27.5% (11/40)	Not statistically significant

Clinical Global Impression scale – Severity scale; proportion of patients classified as 'improved'

	Active deep TMS	Sham deep TMS	p
At end of treatment	61.0% (25/41)	32.6% (14/43)	0.022
4-week follow up	64.1% (25/39)	45.0% (18/40)	Not statistically significant

Mean Sheehan Disability score – decrease from baseline to end of treatment

- Active deep TMS=3.8 (95% CI 1.5 to 6.1)
- Sham deep TMS=3.0 (95% CI 0.8 to 5.3), p=not significant

Blinding assessment

66% of patients in the active treatment group and 69% of patients in the sham treatment group were not aware of or incorrectly guessed the type of treatment they had.

Safety

Adverse events

- Active deep TMS=72.9% (n=35/48)
- Sham deep TMS=68.6% (n=35/51), p=0.639

The authors stated that the adverse events were typical of those reported in TMS studies, the most frequent being headache.

Headache

- Active deep TMS=37.5%
- Sham deep TMS=35.3%

1 serious adverse event was reported: after 2 treatment sessions, 1 patient in the active treatment group reported having significant suicidal thoughts, which had preceded the start of the treatment sessions. The investigator and the patient decided that hospital admission would be appropriate. The patient reported that the suicidal thoughts were related to escalating problems with his family and not to the study treatments.

Dropout rate

- Active deep TMS=12.5% (6/48)
- Sham deep TMS=11.8% (6/51)

Abbreviations used: CI, confidence interval; SSRI, selective serotonin reuptake inhibitor; TMS, transcranial magnetic stimulation; Y-BOCS, Yale-Brown Obsessive Compulsive Scale

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Study 3 Carmi L (2018)

Details

Study type	**Randomised controlled trial**
Country	Israel
Recruitment period	2012 to 2014
Study population and number	**n=41 (18 high-frequency deep TMS, 8 low-frequency deep TMS, 15 sham)** Patients with OCD who met stage III criteria (failure of 2 SSRI trials plus cognitive behavioural therapy)
Age and sex	• High-frequency deep TMS: mean 36 years; 56% (9/16) male • Low-frequency deep TMS: mean 28 years; 50% (4/8) male • Sham TMS: mean 35 years; 50% (7/14) male
Patient selection criteria	Inclusion criteria: age between 18 and 65 years, current Diagnostic and Statistical Manual of Mental disorders (DSM-IV) diagnosis of OCD, Y-BOCS score of 20 or more, cognitive behavioural therapy at maintenance phase (if used); stable SSRI medications maintenance for 8 weeks before enrolment and unchanged during treatment. Exclusion criteria included any other axis I psychopathology or a current depressive episode.
Technique	**High- or low-frequency deep TMS** Deep TMS was administered using a Magstim rapid TMS stimulator (The Magstim Co. Ltd, UK) equipped with an H7-coil (specifically designed to stimulate the anterior cingulate cortex). The coil was aligned symmetrically over the medial prefrontal cortex. High-frequency (20 Hz) TMS was delivered at 100% of the leg resting motor threshold. Sessions consisted of 50 trains lasting 2 seconds each, with an intertrain interval of 20 seconds (2,000 pulses in total). Low-frequency (1 Hz) TMS was delivered at 110% of the leg resting motor threshold. Sessions consisted of 900 consecutive pulses. Sham stimulation was done using a sham coil and was randomised to mimic either high or low frequency. A symptom provocation was done before each treatment, with the aim of achieving a self-reported distress score of 4 to 7 out of 10. All groups had 5 sessions per week for 5 weeks (a total of 25 sessions).
Follow up	**1 month**
Conflict of interest/source of funding	The study was partially supported by Brainsway, which produces the deep TMS H-coil systems. One of the authors is a co-inventor of the TMS H-coils and serves as consultant for and has financial interests in Brainsway.

Analysis

Follow-up issues: Of the 41 randomised patients, 3 dropped out during treatment: 1 because of conflicting schedule (sham group) and 2 because of inconvenience with the treatment (high-frequency group). The final analysis included the 93% (38/41) of patients who completed the treatment.

Study design issues: Prospective, single-centre double-blind randomised controlled trial. Patients were recruited through newspaper and web advertisements and the study centre's outpatient programme. Computerised randomisation was used to assign each patient to a treatment group. Patients, operators and raters were blind to treatment allocation. The primary outcome measure was the change in Y-BOCS score from baseline. A clinical response was defined as a reduction of 30%. For the Clinical Global Impression – improvement secondary outcome measure, response was defined as a score of 2 or less (very much improved or much improved).

An interim analysis was done midway through the study and the low-frequency group was subsequently excluded because of a lack of consistent response and limited rate of recruitment of the study population.

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Study population issues: There were no statistically significant differences in baseline characteristics between the 3 groups.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 30 (16 high-frequency deep TMS, 14 sham)

Y-BOCS - response rate after 5 weeks of treatment (30% reduction in Y-BOCS relative to baseline)
<table>
<tr><th></th><th>High-frequency deep TMS</th><th>Sham deep TMS</th><th>p</th></tr>
<tr><td>At end of treatment</td><td>43.8% (7/16)</td><td>7.1% (1/14)</td><td><0.05</td></tr>
<tr><td>1-week follow up</td><td>45.5% (5/11)</td><td>7.7% (1/13)</td><td><0.05</td></tr>
<tr><td>1-month follow up</td><td>44.4% (4/9)</td><td>0% (0/9)</td><td><0.05</td></tr>
</table>
Proportion of patients with 35% reduction or more in Y-BOCS after 5 weeks of treatment

High-frequency deep TMS=29.4% (5/16)
Sham=7.1% (1/14), p<0.10

Clinical Global Impressions scale – Improvement scale; proportion of patients with a score of 2 or less (very much improved or much improved)
<table>
<tr><th></th><th>Active deep TMS</th><th>Sham deep TMS</th><th>p</th></tr>
<tr><td>At end of treatment</td><td>68.8% (11/16)</td><td>7.1% (1/14)</td><td><0.001</td></tr>
<tr><td>1-week follow up</td><td>63.6% (7/11)</td><td>7.7% (1/13)</td><td><0.01</td></tr>
<tr><td>1-month follow up</td><td>55.6% (5/9)</td><td>33.3% (3/9)</td><td><0.35</td></tr>
</table>
Most patients did not guess which group they were assigned to.
</td><td>
There were no severe adverse events.

Side effects (including headaches and fatigue)

High-frequency deep TMS=18.8% (3/16)
Sham=7.1% (1/14)

</td></tr>
<tr><td colspan="2">Abbreviations used: TMS, transcranial magnetic stimulation; Y-BOCS, Yale-Brown Obsessive Compulsive Scale</td></tr>
</table>

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Study 4 Singh S (2019)

Details

Study type	**Case series**
Country	India
Recruitment period	2010 to 2016
Study population and number	**n=79** Patients with OCD
Age and sex	Mean 32 years; 60% (47/79) male
Patient selection criteria	Inclusion criteria: patients older than 18 years with primary diagnosis of OCD confirmed on clinical interview by a psychiatrist (according to the International Classification of Diseases, tenth edition criteria), with failure to respond to at least 2 first-line anti-obsessional drug trials at adequate dose and duration. Exclusion criteria: patients with any comorbid psychiatric disorder other than depression, history of seizures, neurosurgical metallic implant, cardiac pacemaker or inner ear prosthesis, pregnancy or unstable medical condition.
Technique	**Low-frequency rTMS** Device: Magstim Rapid stimulator (Magstim Company Ltd., UK) Stimulation parameters: 1 Hz frequency, 110% of resting motor threshold, 5 second train duration, intertrain interval of 10 seconds, and 240 trains per session. A total of 20 sessions of rTMS, 5 days per week over a period of 4 weeks were delivered. The site of stimulation was the bilateral SMA (58%) or left OFC (42%). Patients were continued on their last drug combination, which they were having for at least 12 weeks before and during the study period.
Follow up	**After 20 sessions**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Patients were only included if they had had 20 sessions of rTMS. Outcomes were measured after the 20 sessions were completed.

Study design issues: Retrospective, single-centre case series. The main outcome measure was the Y-BOCS. Response was classified as full response (35% or greater reduction in Y-BOCS score from baseline) and partial response (25% or greater reduction in Y-BOCS score from baseline).

Study population issues: The mean duration of illness was 11 years. 52% of patients had a comorbid major depressive episode. The mean number of failed drug trials at baseline was 3.

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Key efficacy and safety findings

Efficacy

Number of patients analysed: **79**

Mean Y-BOCS score

- At baseline=28.47±5.57
- After 20 rTMS sessions=20.78±8.08

Paired differences (mean±SD)=7.68±5.62, 95% CI 6.42 to 8.94, p<0.001

- Partial response (reduction in score of 25% or more)=57% (45/79)
- Complete response (reduction in score of 35% or more)=40.5% (32/79)

Comparison of demographic and clinical characteristics between 2 groups divided on the basis of response to rTMS

Variable	Responders (n=32) Mean±SD/frequency (%)	Non-responders (n=47) Mean±SD/frequency (%)	p
Sex			0.62
Male	18 (38.3%)	29 (61.7%)	
Female	14 (43.8%)	18 (56.2%)	
Age of illness onset, years	20.72±5.13	21.04±5.80	0.80
Total duration of illness, years	8.25±5.14	12.96±7.93	0.002
Baseline Y-BOCS score	25.97±6.32	30.17±4.28	0.002
Site of stimulation			0.76
SMA	18 (39.1%)	28 (60.9%)	
OFC	14 (42.4%)	19 (57.6%)	
Comorbid MDE			0.01
Yes	11 (26.8%)	30 (73.2%)	
No	21 (55.3%)	17 (44.7%)	
No. failed drug trials			0.01
Up to 2	18 (58.1%)	13 (41.9%)	
More than 2	14 (29.2%)	34 (70.8%)	

Summary of binary logistic regression results

Variable	B	SE	Wald	df	p	Exp (B)
Total duration of illness, years	−0.079	0.046	2.950	1	0.086	1.082
Baseline Y-BOCS score	−0.130	0.058	5.062	1	0.024	1.139
More than 2 failed drug trials	−1.100	0.576	3.651	1	0.056	3.004
Comorbid MDE	−1.301	0.568	5.244	1	0.022	3.675
Constant	5.395	1.710	9.956	1	0.002	0.005

Safety

Adverse effects

- Headache=12.7% (10/79)
- Localised scalp discomfort=16.5% (13/79)

Abbreviations used: B, Bonferroni coefficient; df, degrees of freedom; Exp (B), exponential beta (odds ratio); MDE, major depressive episode; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; SE, standard error; SMA, supplementary motor area; Y-BOCS, Yale-Brown Obsessive Compulsive Scale

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Study 5 Arumugham S (2018)

Details

Study type	**Randomised controlled trial**
Country	India
Recruitment period	2013 to 2015
Study population and number	**n=40 (20 active low-frequency rTMS, 20 sham)** Patients with OCD
Age and sex	• Active low-frequency rTMS: mean 28 years; 84% (16/19) male • Sham: mean 31 years; 71% (12/17) male
Patient selection criteria	Inclusion criteria: age 18 years or older, OCD of at least 1-year duration, adequate trial of at least 1 SSRI, clinically significant symptoms despite adequate trials with SSRIs (Y-BOCS 16 or above, CGI – Improvement score 4 or above), stable dose of SSRI for at least 8 weeks. Patients with contraindications for rTMS (intracranial metallic implants, pacemakers, primary seizure disorder), comorbid psychotic or bipolar disorder, severe depression (defined as HAM-D score higher than 23) and active suicidality as assessed with the Mini-International Neuropsychiatric Interview, comorbid active substance use (apart from nicotine use disorder), concomitant behaviour therapy, and those with unstable medical conditions, pregnancy, and breastfeeding were excluded from the study.
Technique	Device: MagPro R100; MagVenture, Denmark) **Low-frequency rTMS** was delivered over the presupplementary motor area (pre-SMA). Stimulation parameters: 1,200 stimuli per day given at 1 Hz in 4 trains of 300 seconds each, with intertrain intervals of 2 minutes, at 100% resting motor threshold. Sham treatment was done with the same parameters but using a sham coil. Treatment consisted of 18 daily sessions, delivered over a period of 3 weeks (excluding Sundays).
Follow up	**End of treatment**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Of the 40 randomised patients, 36 (90%) were included in the analysis: 1 patient in the active treatment group was excluded because they did not divulge comorbidity or bipolar disorder, 2 patients in the sham group withdrew consent before baseline assessment and 1 did not follow protocol. Of the 36 patients included in the analysis, 1 patient in each group dropped out before study completion: the patient in the active group had no improvement and the patient in the sham group dropped out because of headache.

Study design issues: Prospective, single-centre randomised controlled trial. Computer-generated randomisation and sealed opaque envelopes were used to allocate patients to each treatment group. Patients and raters were blinded to the treatment allocation. The planned sample size was 70, to give a power of 80%, but only 40 patients could be randomised during the study period. The primary outcome measure was the change in Y-BOCS scores. A decrease in Y-BOCS of 35% or more was considered to be a response.

Study population issues: There were no statistically significant differences in relevant demographic and clinical variables between the 2 groups at baseline.

Other issues: The main reason for declining study participation was the difficulty in attending daily sessions for 3 weeks.

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Key efficacy and safety findings

Efficacy

Number of patients analysed: **36 (19 active rTMS, 17 sham)**

Clinical outcomes

Scale	Active, mean (SD)	Sham, mean (SD)	ANOVA time effect		ANOVA group*time interaction	
			F	p	F	p
Y-BOCS						
Week 0	25.05 (5.32)	26.06 (6.01)	15.909	<0.01	0.80	0.48
Week 1	22.58 (5.61)	23.65 (6.74)				
Week 2	20.84 (5.35)	23.59 (6.87)				
Week 3	19.26 (6.92)	21.82 (7.51)				
CGI-S						
Week 0	4.47 (0.70)	4.71 (0.77)	13.53	<0.01	0.31	0.82
Week 1	3.40 (0.91)	3.53 (1.07)				
Week 2	4.05 (0.71)	4.24 (1.39)				
Week 3	3.79 (0.79)	4.18 (1.07)				
HAM-D						
Week 0	8.11 (5.64)	8.18 (3.17)	1.95	0.13	0.20	0.88
Week 1	7.26 (5.59)	7.35 (6.89)				
Week 2	6.11 (4.88)	6.65 (6.28)				
Week 3	7.53 (7.97)	6.94 (5.31)				
HAM-A						
Week 0	6.21 (5.02)	6.47 (5.69)	3.67	0.04	0.31	0.82
Week 1	4.79 (3.92)	5.82 (6.85)				
Week 2	4.21 (3.90)	5.47 (5.79)				
Week 3	4.21 (3.77)	5.18 (4.64)				

Percentage reduction in Y-BOCS scores at end of treatment

- Active rTMS=23.54
- Sham=15.24, p=0.27

Response rate at end of treatment (35% or more decrease in Y-BOCS)

- Active rTMS=31.6% (6/19)
- Sham=17.7% (3/17), p=0.451

Safety

There were no serious adverse events, including seizures.

The most commonly reported adverse effects over the course of treatment were headache, sedation, concentration difficulties, and failing memory. The prevalence of these adverse effects was not statistically significantly different between the 2 groups.

Abbreviations used: ANOVA, analysis of variance; CGI-S, Clinical Global Impression – Severity; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; OCD, obsessive-compulsive disorder; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; SMA, supplementary motor area; SSRI, selective serotonin reuptake inhibitor; Y-BOCS, Yale-Brown Obsessive Compulsive Scale

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Study 6 Zhang K (2019)

Details

Study type	**Randomised controlled trial**
Country	China
Recruitment period	Not reported
Study population and number	**n=57 (28 active rTMS, 29 sham rTMS)** Patients with OCD
Age and sex	• Active rTMS: mean 32 years; 60% (15/25) male • Sham: mean 39 years; 58% (14/24) male
Patient selection criteria	Inclusion criteria: diagnosis of current OCD by a psychiatrist in accordance with DSM-IV on the basis of a structured clinical interview for DSM; patients were not on medication; patients were willing and able to consent to the study on the basis of their ability to provide a spontaneous narrative description of its key elements; after a careful neurological interview and inspection of medical records, so seizures or further neurological disorders or major medical issues were reported or recorded; absence of comorbid psychiatric disorders; no current alcohol and other drug use; age between 18 and 65 years. Exclusion criteria: inclusion criteria above not met; patient had metal implants; female patients were pregnant, breastfeeding or intending to become pregnant during the period of the study; history of DSM-IV substance dependence in the past 6 months; acute suicidality; patients experienced severe adverse effects during or after the treatment or if the patient withdrew from the study for any reason. Patients who had previous experience of active rTMS were also excluded.
Technique	**Low-frequency rTMS** Device: Magstim super-rapid stimulator (Magstim Company Ltd., UK) with a focal 8-shaped coil. Stimulation parameters were 1 Hz, 20-minute trains (1,200 pulses/day) at 100% of the resting motor threshold, once per day, 5 days per week, for 4 weeks. The coil was positioned over the pre-SMA. Sham treatment was done using a sham coil, which had a metal plate inside it to prevent the magnetic coil from stimulating the cortex. The coil looks and sounds like the active one, but it does not produce the same tapping sensation on the scalp that it is produced with active rTMS. All patients had adequate dosages of SSRIs for at least 4 weeks; these were started on the first day of the study and then gradually increased as directed by psychiatrists.
Follow up	**End of treatment**
Conflict of interest/source of funding	One author received research supports from Otsuka, Sumitomo-Dainippon and Taisho. The authors reported no other conflicts of interest.

Analysis

Follow-up issues: Of the 57 randomised patients, 8 dropped out before the end of the study (3 in the active group and 5 in the sham group).

Study design issues: Randomised, double-blind, controlled trial. Patients were randomised to a treatment group using a computer-generated schedule. The interviewing psychiatrist and the patients were all blinded to the treatment allocation. Assessments were done using the Y-BOCS, the 17-item HAM-D and the HAM-A. A positive response to treatment was defined as a 25% decrease in the Y-BOCS total score. Genotyping was also done to assess the effect of genotyping on rTMS efficacy.

Study population issues: There were no statistically significant differences in baseline demographic and clinical data between the 2 groups. The mean Y-BOCS scores at baseline were 17.2 in the active rTMS group and 18.1 in the sham group.

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Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 49 (25 active rTMS, 24 sham)

Assessment scores after treatment, mean±SD
<table>
<tr><td colspan="2"></td><td>Baseline</td><td>Week 2</td><td>Week 4</td><td colspan="3">Analyses (p values)</td></tr>
<tr><td colspan="2"></td><td colspan="3"></td><td>ME time</td><td>ME rTMS</td><td>Interaction</td></tr>
<tr><td>Y-BOCS</td><td>Active</td><td>17.24±4.27</td><td>13.44±4.64</td><td>11.72±3.78**</td><td>0.00</td><td>0.04</td><td>0.16</td></tr>
<tr><td></td><td>Sham</td><td>18.08±4.43</td><td>16.08±4.54</td><td>14.58±3.72**</td><td colspan="3"></td></tr>
<tr><td>HAM-A</td><td>Active</td><td>12.76±9.34</td><td>9.32±7.99</td><td>8.12±7.79</td><td>0.00</td><td>0.73</td><td>0.06</td></tr>
<tr><td></td><td>Sham</td><td>10.13±6.30</td><td>9.50±5.42</td><td>8.58±5.54</td><td colspan="3"></td></tr>
<tr><td>HAM-D</td><td>Active</td><td>16.16±9.54</td><td>12.52±8.79</td><td>8.36±8.19**</td><td>0.00</td><td>0.95</td><td>0.06</td></tr>
<tr><td></td><td>Sham</td><td>13.96±6.31</td><td>12.17±4.55</td><td>10.58±4.81*</td><td colspan="3"></td></tr>
</table>
**p<0.01 compared with baseline, *p<0.05 compared with baseline

Effect of genotype on rTMS efficacy – genotyping of 5-HTTLPR (serotonin-transporter-linked promoter region) in the SLC6A4 gene (long [L] or short [S] variant)
Of the 25 patients in the active group, 4 had the LL genotype, 12 had the SS genotype and 9 had the SL genotype.
Of the 24 patients in the sham group, 3 had the LL genotype, 13 had the SS genotype and 8 had the SL genotype.
There was a statistically significantly greater improvement in Y-BOCS score in the active group with the LL genotype compared with the sham group with the LL genotype.
There was no statistically significant improvement in S allele carriers.</td><td>The most frequently reported adverse effects were headache, localised scalp pain, and dizziness.</td></tr>
<tr><td colspan="2">Abbreviations used: DSM, Diagnostic and Statistical Manual of Mental disorders; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; ME time, main effect of time; ME rTMS, main effect of rTMS status; OCD, obsessive-compulsive disorder; SD, standard deviation; SMA, supplementary motor area; SSRI, selective serotonin reuptake inhibitor; Y-BOCS, Yale-Brown Obsessive Compulsive Scale</td></tr>
</table>

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Study 7 Badawy A (2010)

Details

Study type	**Randomised controlled trial**
Country	Egypt
Recruitment period	2008
Study population and number	**n=60 (20 rTMS as add-on treatment, 20 rTMS as monotherapy, 20 sham)** Patients with OCD
Age and sex	• Add-on rTMS: mean 28 years; 60% (12/60) male • Monotherapy rTMS: mean 26 years; 50% (10/20) male • Sham rTMS: mean 29 years; 35% (7/20) male
Patient selection criteria	All patients were diagnosed with OCD according to Diagnostic and Statistical Manual of Mental disorders (DSM-IV) criteria. Two groups of patients had never had medication for their OCD (the monotherapy and sham groups). The third group of patients had symptoms that responded poorly to SSRIs. Exclusion criteria: patients with comorbid depression or other psychiatric disorders, patients with epilepsy or history or other neurological disorders that might be epileptogenic (for example brain tumour, history of meningitis, encephalitis, or severe head trauma), patients with cardiac pacemaker or any other implanted electronic device, and pregnant women.
Technique	**High-frequency rTMS** (20 Hz) was used to stimulate the left dorsolateral prefrontal cortex for 5 sessions per week for 3 successive weeks. Sham stimulation was applied by angling the coil off the head so that the magnetic field stimulated the superficial scalp muscles but did not enter the brain. It simulated the sensation and acoustic properties of rTMS.
Follow up	**End of treatment**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Losses to follow up were not described.

Study design issues: Randomised, double-blind, controlled trial. Forty patients who had never had medication for OCD were randomly assigned to active (even numbers) or sham rTMS (odd numbers). A third group of 20 patients with symptoms that responded poorly to SSRIs were offered active rTMS. The patients did not know whether they had sham or active rTMS and the researchers who did the clinical assessment were unaware of what treatment the patient had (sham, active, or medicated groups). Y-BOCS was used to assess the severity of OCD symptoms before the first treatment session and after 15 sessions were completed. A reduction in Y-BOCS scores of more than 40% was considered to be a clinically significant improvement.

Study population issues: Patients had either combined obsession and compulsion (63%) or only compulsions (37%). The baseline Y-BOCS score was higher in the add-on group than the other 2 groups, but this was not discussed in the paper and no statistical analysis was reported.

This study is included in the systematic review by Rehn et al. (2018; study 1).

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Key efficacy and safety findings

Efficacy

Number of patients analysed: **60 (20 add-on active rTMS, 20 active monotherapy rTMS, 20 sham)**

Response to rTMS

Response	Add-on group	Monotherapy group	Sham group	p1*	p2*	p3*
Good	11 (55%)	5 (25%)	1 (5%)	0.07	0.05	0.006
None	9 (45%)	15 (75%)	19 (95%)			

p1=difference between sham group and monotherapy group

p2=difference between monotherapy and add-on treatment group

p3=difference between sham group and add-on treatment group

YBCOS scores before and after rTMS, mean±SD

	Y-BOCS score before rTMS	Y-BOCS score after rTMS	p
Add-on group	25.85±4.88	20.60±4.30	0.001
Monotherapy group	22.65±4.42	20.80±3.66	0.16
Sham group	22.95±3.63	21.65±3.01	0.23

Motor threshold before and after rTMS, mean±SD

	Motor threshold before rTMS	Motor threshold after rTMS	p
Add-on group	63.9±8.1	69.5±7.6	0.03
Monotherapy group	71.0±8.8	80.2±8.3	0.002
Sham group	71.0±8.8	71.6±8.8	0.8

Motor threshold before and after rTMS according to treatment response, mean±SD

	Motor threshold before rTMS	Motor threshold after rTMS	p
Good response to rTMS (n=15)	67.1±8.7	79.1±8.9	0.001
Poor response to rTMS (n=25)	67.9±9.6	72.2±9.1	0.11

Safety

No safety data were reported.

Abbreviations used: OCD, obsessive-compulsive disorder; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; Y-BOCS, Yale-Brown Obsessive Compulsive Scale

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Study 8 Pallanti S (2016)

Details

Study type	**Randomised controlled trial**
Country	Italy
Recruitment period	Not reported
Study population and number	**n=50 (25 rTMS, 25 TAU - antipsychotic augmentation)** Patients with SSRI-refractory OCD
Age and sex	• rTMS: mean 34 years; 52% (13/25) male • TAU: mean 33 years; 52% (13/25) male
Patient selection criteria	Inclusion criteria: Diagnostic and Statistical Manual of Mental disorders (DSM-IV) diagnosed OCD, age 18 or older, Y-BOCS score of 16 or above and no or insufficient response after at least 2 trials (8 weeks) with SSRIs and 1 trial with clomipramine and 1 trial with CBT (15 sessions) as indicated by a lack of a statistically significant reduction in Y-BOCS score (>35%). Exclusion criteria: substance abuse or dependence within the last year, risk of seizure or epilepsy, implanted devices, metal in the brain, pregnancy, and neurological disorders.
Technique	**Low-frequency rTMS** (1 Hz) Device: Magstim rapid stimulator (Magstim Company Ltd., UK) with an 8-shaped coil was used for bilateral stimulation of the SMA. Stimulation parameters: 1 Hz, 1,200 pulses per day at 100% of resting motor threshold, once a day, 5 days a week for 3 weeks (15 sessions in total). TAU group: antipsychotic medication Medication type and dose were stable for at least 8 weeks before the study and remained stable throughout the trial.
Follow up	**End of treatment**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: The outcome measurements were done at baseline, after 8 TMS stimulations and at the end of the third week.

Study design issues: Randomised controlled open-label trial. Consecutively admitted patients were randomly assigned to rTMS according to a computer-generated schedule. Patients assigned to the other group had TAU (with antipsychotic medication). The raters were blind to the treatment allocation. The primary outcome measure was the reduction of disease severity according to Y-BOCS. The response rate was a secondary outcome, defined as a decrease of 25% or more in Y-BOCS total score compared with baseline. Remission was defined as a Y-BOCS score of 11 or less. All analyses were done on the modified intention-to-treat population, which included all randomised patients who had at least 1 week of treatment and completed at least 1 follow-up Y-BOCS assessment.

Study population issues: The 2 treatment groups were not statistically significant at baseline. Comorbidities included eating disorder (n=6), attention deficit hyperactivity disorder (n=1), unipolar mood disorder (n=1), panic disorder (n=7), bipolar mood disorder (n=5), depression (n=4), and OCD (n=1).

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Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 50 (25 rTMS, 25 TAU)

Mean Y-BOCS scores
<table>
<tr><th></th><th>rTMS</th><th>TAU</th></tr>
<tr><td>Baseline</td><td>30.16</td><td>31.44</td></tr>
<tr><td>After 3 weeks</td><td>20.92</td><td>25.56</td></tr>
<tr><td>p</td><td><0.0005</td><td><0.0005</td></tr>
</table>
Y-BOCS - response rate
• rTMS=68% (17/25)
• TAU=24% (6/25)

Y-BOCS - remission rate
• rTMS=12% (3/25)
• TAU=0% (0/25)

17.6% (3/17) of patients whose symptoms responded to rTMS achieved remission.</td><td>There were no dropouts; none of the patients had seizures or syncope, neurological complications or other major adverse effects.</td></tr>
<tr><td colspan="2">Abbreviations used: CBT, cognitive behavioural therapy; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor TAU, treatment as usual; Y-BOCS, Yale-Brown Obsessive Compulsive Scale</td></tr>
</table>

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Study 9 Tendler A (2018)

Details

Study type	**Review**
Country	US
Recruitment period	2010 to 2018
Study population and number	**n=33 (2 with OCD)** Patients who had seizures or pseudo-seizures after deep rTMS
Age and sex	The patients with OCD were a 59-year-old woman and an 18-year-old man
Patient selection criteria	Seizures or pseudo-seizures reported in the literature or to the manufacturer, spontaneously or in response to active survey.
Technique	**Deep rTMS** Device: H-coil deep rTMS (Brainsway Ltd, Israel).
Follow up	**None**
Conflict of interest/source of funding	All 3 authors have a financial interest in Brainsway Ltd, the manufacturer of the deep rTMS system.

Analysis

Study design issues: The rate of seizures was assessed based on the number of personal head caps that were purchased and used for each patient's entire course of treatment. The overall crude rate was calculated and the per instructions for use rate, which excluded cases where the motor threshold was not rechecked in the last week or after medication changes, binge drinking episodes, sleep deprivation and previously known neurological injury.

Study population issues: Of the 33 patients, most had treatment for depression. Two patients had treatment for OCD, 1 of whom also had depression and panic disorder.

Key efficacy and safety findings

Safety
Overall crude seizure rate=0.00087 (based on sales of 35,443 personal head caps) Per instructions for use rate=0.00028 (10/35,443) (1 resulted in diagnosis of a brain tumour) No seizures happened during the first deep rTMS treatment session. Most seizures appeared to have multiple proximal risk factors, including not rechecking the motor threshold, increased alcohol intake and withdrawal, changes in medication, poor sleep and exaggerated caffeine intake. All of the seizures were self-limiting, ictal activity ranging from 20 to 120 seconds with varied post ictal periods. In 1 patient with depression, OCD and panic disorder, the deep rTMS was applied at 140% motor threshold. The patient subsequently had high-frequency rTMS. In the second patient with OCD, the deep rTMS was applied at 100% motor threshold. The patient had a pseudo-seizure with no loss of consciousness and both eyes blinking.
Abbreviations used: OCD, obsessive-compulsive disorder; rTMS, repetitive transcranial magnetic stimulation

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Validity and generalisability of the studies

- There were data from North America, Africa, Asia, Europe and Australia.
- Most of the RCTs included in the meta-analysis were small (the number of patients ranged from 10 to 46).
- Many of the RCTs were heterogenous for clinical variables and stimulation parameters.
- Sham coils may produce a larger placebo effect than tilted coils because they can produce auditory and somatic sensations similar to an active coil.
- Some studies used low-frequency rTMS and others used high-frequency TMS. Two studies used deep TMS.[2,3]
- Different areas were targeted for stimulation within and between studies.
- The definition of response varied between studies.
- Some studies excluded patients with comorbid depression. In those studies that included patients with comorbid anxiety and depression, some improvement in OCD symptoms could be secondary to improvements in anxiety and depression.
- Most studies only reported outcomes at the end of treatment and the longest follow up was 12 weeks.
- Most patients had chronic and resistant OCD with symptoms that had failed to respond to medication.

Existing assessments of this procedure

In 2013, the Canadian Agency for Drugs and Technologies in Health published a rapid response report on 'Repetitive Transcranial Magnetic Stimulation for Specific Patient Populations: Clinical and Cost-Effectiveness and Safety'.[10] The report identified 3 relevant RCTs for OCD, with patient numbers between 21 and 30. The report concluded:

'*For patients with auditory hallucination or obsessive compulsive disorder there appears to be no significant improvement with rTMS treatment of duration >2 weeks or >10 sessions when compared to sham. No relevant evidence was*

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identified for substance use disorders. Generally, the side effects with rTMS were mild and there appear to be no issues with respect to tolerance of the procedure. No robust evidence was identified on the cost effectiveness of rTMS compared with sham or pharmacotherapy.

Several factors such as comorbidities, concomitant medication, refractoriness to pharmacotherapy, disease condition and individual patient characteristics may impact outcomes with rTMS and may be worth considering when deciding on an optimal treatment strategy.'

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Transcranial magnetic stimulation for treating and preventing migraine. NICE interventional procedures guidance 477 (2014). Available from http://www.nice.org.uk/guidance IPG477
- Repetitive transcranial magnetic stimulation for depression. NICE interventional procedures guidance 542 (2015). Available from http://www.nice.org.uk/guidance IPG542

NICE guidelines

- Obsessive-compulsive disorder and body dysmorphic disorder: treatment. NICE clinical guideline 31 (2005). Available from http://www.nice.org.uk/guidance/CG31

Additional information considered by IPAC

Professional experts' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public

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consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three Professional Expert Questionnaires for transcranial magnetic stimulation for obsessive-compulsive disorder were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 2 companies who manufacture a potentially relevant device for use in this procedure. NICE received 2 completed submissions. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials:

- Repetitive Transcranial Magnetic Stimulation in Obsessive Compulsive Disorder (MAGTOC) (NCT02884674); France; RCT; n=57; estimated completion date May 2020.
- A Randomized Clinical Trial of Repetitive Transcranial Magnetic Stimulation (rTMS) Treatment for Obsessive-Compulsive Disorder (NCT03649685); China; n=120; estimated completion date October 2021.
- Study of Brain Network Mechanism for Individualized Accurate Target Positioning rTMS Treatment on Obsessive Compulsive Disorder (NCT03393078); China; RCT; n=60; estimated completion date April 2019.
- rTMS Over the Supplementary Motor Area for Treatment-resistant Obsessive-compulsive Disorder: a Multicenter, Double-blind, Controlled Trial

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(NCT03211221); Italy; RCT; n=30; estimated completion date December 2019.

- Testing the Causal Role of Orbitofrontal Cortex in Human Compulsive Behavior: a Non-invasive Brain Stimulation Study (NCT03265015); US; RCT; n=70; estimated completion date March 2020.
- Effects of rTMS Over Right COF Blood Perfusion in OCD Patients: an ASL Double Blinded Study (NCT03918837); France; RCT; n=30; estimated completion date November 2020.
- Neuromodulation Enhanced Cognitive Restructuring: A Proof of Concept Study (NCT02573246); US; RCT; n=105; estimated completion date April 2020.

  Neurocircuitry of Obsessive-Compulsive Disorder: Modulation by Transcranial Magnetic Stimulation (NCT02704117); US; case series; n=30; estimated completion date May 2020.

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References

1. Rehn S, Eslick GD, Brakoulias V (2018) A meta-analysis of the effectiveness of different cortical targets used in repetitive transcranial magnetic stimulation (rTMS) for the treatment of obsessive-compulsive disorder (OCD). The Psychiatric Quarterly 89: 645–65
2. Carmi L, Tendler A, Bystritsky A et al. (2019) Efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder: a prospective multicenter randomized double-blind placebo-controlled trial. The American Journal of Psychiatry doi: 10.1176/appi.ajp.2019.18101180
3. Carmi L, Alyagon U, Barnea-Ygael N et al. (2018) Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients. Brain Stimulation 11: 158–65
4. Singh S, Kumar S, Gupta A et al. (2019) Effectiveness and predictors of response to 1-hz repetitive transcranial magnetic stimulation in patients with obsessive-compulsive disorder. The Journal of ECT 35: 61–6
5. Arumugham SS, Vs S, Hn M et al. (2018) Augmentation effect of low-frequency repetitive transcranial magnetic stimulation over presupplementary motor area in obsessive-compulsive disorder: a randomized controlled trial. The Journal of ECT 34: 253–7
6. Zhang K, Fan X, Yuan J et al. (2019) Impact of serotonin transporter gene on rTMS augmentation of SSRIs for obsessive compulsive disorder. Neuropsychiatric Disease and Treatment 15: 1771–9
7. Badawy AA, El Sawy H, Abd El Hay M (2010) Efficacy of repetitive transcranial magnetic stimulation in the management of obsessive compulsive disorder. Egyptian Journal of Neurology, Psychiatry and Neurosurgery 47: 393–8
8. Pallanti S, Marras A, Salerno L et al. (2016) Better than treated as usual: transcranial magnetic stimulation augmentation in selective serotonin reuptake inhibitor-refractory obsessive-compulsive disorder, mini-review and pilot open-label trial. Journal of Psychopharmacology 30: 568–78
9. Tendler A, Yiftach R, Abrah Z (2018). Rate of inadvertently induced seizures with deep repetitive transcranial magnetic stimulation. Brain Stimulation 11: 1410–4
10. Canadian Agency for Drugs and Technologies in Health (2013). Repetitive Transcranial Magnetic Stimulation for Specific Patient Populations: Clinical and Cost-Effectiveness and Safety. CADTH Rapid Response Service.

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Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	17/07/2019	Issue 7 of 12, July 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	17/07/2019	Issue 7 of 12, July 2019
HTA database (CRD website)	17/07/2019	n/a
MEDLINE (Ovid) & MEDLINE In-Process (Ovid)	17/07/2019	1946 to July 16, 2019
MEDLINE ePubs ahead of print (Ovid)	17/07/2019	July 16, 2019
EMBASE (Ovid)	17/07/2019	1974 to 2019 July 16
BLIC	17/07/2019	n/a

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- 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.

1	Transcranial Magnetic Stimulation/ (10526)
2	((transcran* or deep* or repetit*) adj4 magnet* adj4 stimulat*).tw. (11730)
3	((deep* or repetit*) adj4 transcran* adj4 stimulat*).tw. (3553)
4	(TMS or rTMS or dTMS).tw. (11680)
5	or/1-4 (17302)
6	Obsessive-Compulsive Disorder/ (13820)
7	OCD.tw. (7495)
8	anankastic*.tw. (49)

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9	obsess*.tw. (16777)
10	compuls*.tw. (26676)
11	or/6-10 (33331)
12	5 and 11 (180)
13	Brainsway*.tw. (8)
14	Tranquality*.tw. (0)
15	SmartTMS*.tw. (0)
16	MagVenture*.tw. (5)
17	Ectron*.tw. (5)
18	or/12-17 (198)
19	animals/ not humans/ (4566289)
20	18 not 19 (195)
21	limit 20 to english language (181)

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Appendix

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

Case reports were excluded, unless they reported a safety event.

Article	Number of patients/ Follow up	Direction of conclusions	Reasons for non-inclusion in table 2
Alonso P, Pujol J, Cardoner N et al. (2001) Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a double-blind, placebo-controlled study. The American Journal of Psychiatry 158: 1143–5	RCT n=18	Low-frequency rTMS of the right prefrontal cortex failed to produce a statistically significant improvement of OCD and was not statistically significantly different from sham treatment. Further studies are indicated to assess the efficacy of rTMS in OCD and to clarify the optimal stimulation characteristics.	Small RCT, included in the systematic review by Rehn et al. (2018).
Aydin EP, Kenar JG, Altunay IK et al. (2019) Repetitive transcranial magnetic stimulation in the treatment of skin picking disorder: An exploratory trial. The Journal of ECT doi: 10.1097/YCT.0000000000000616.	RCT n=15	Treatment response was achieved in 63% of patients (5/8) in the active group and 33% of patients (2/6) in the sham group. However, there were no statistically significant differences between the groups in terms of primary and secondary outcomes.	Studies with more patients or longer follow up are included.
Berlim M, Neufeld NH Van den Eynde F (2013) Repetitive transcranial magnetic stimulation (rTMS) for obsessive-compulsive disorder (OCD): an exploratory meta-analysis of randomized and sham-controlled trials. Journal of Psychiatric Research 47: 999–1006	Systematic review and meta-analysis 10 studies	active rTMS seems to be efficacious for treating OCD. Future RCTs on rTMS for OCD should include larger sample sizes and be more homogeneous in terms of demographic/clinical variables as well as stimulation parameters and brain targets.	A more recent systematic review is included (Rehn et al. 2018).
Donse L, Sack AT, Fitzgerald PB et al. (2017) Sleep disturbances in obsessive-compulsive disorder: Association with non-response to repetitive transcranial magnetic stimulation (rTMS). Journal of Anxiety Disorders 49: 31–9	Case series n=22	Circadian rhythm sleep disorders (CRSD) are more prevalent in OCD patients than healthy subjects, specifically in rTMS non-responders. Therefore, CRSD may serve as a biomarker for different subtypes of OCD corresponding with response to specific treatment approaches.	Small case series, focusing on sleep disturbances.
Elbeh KAM, Elserogy YMB, Khalifa HE et al. (2016) Repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorders: Double	RCT n=45 FU=3 months	There was a significant "time"x"group" interaction for 1Hz versus Sham but not for 10Hz versus Sham. 1Hz versus 10Hz groups showed a significant interaction for Y-BOCS and HAM-A (p=0.001 and 0.0001	Included in the systematic review by Rehn et al. (2018).

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blind randomized clinical trial. Psychiatry Research 238: 264–9		respectively). 1Hz rTMS had a greater clinical benefit than 10Hz or sham. There was also a statistically significantly larger percentage change in GCI-S in the 1Hz group versus either 10Hz or sham. We conclude that 1Hz-rTMS, targeting right dorsolateral prefrontal cortex (DLPFC) is a promising tool for treatment of OCD.	
Elmedany AM, Ismail WF, Elgendy HH et al. (2014) Repetitive transcranial magnetic stimulation (rTMS) in obsessive compulsive disorder. Egyptian Journal of Neurology, Psychiatry and Neurosurgery 51: 369–73	Case series n=20	Symptoms in patients with OCD have a better response to rTMS for obsession symptoms more than for compulsions especially those on pharmacological treatment.	Small case series.
Gomes PVO, Brasil-Neto JP, Allam N et al. (2012) A randomized, double-blind trial of repetitive transcranial magnetic stimulation in obsessive-compulsive disorder with three-month follow-up. The Journal of Neuropsychiatry and Clinical Neurosciences 24: 437–43	RCT n=22 FU= 3 months	After 14 weeks, the response rate was 41% (7/12) with active and 10% (1/10) with sham treatment. At 14 weeks, patients who had active rTMS showed, on average, a 35% reduction on the Y-BOCS, as compared with a 6% reduction in those who had sham treatment.	Small RCT, included in the systematic review by Rehn et al. (2018).
Greenberg BD, George MS, Martin JD et al. (1997) Effect of prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a preliminary study. The American Journal of Psychiatry 154: 867–9	Case series n=12	These preliminary results suggest that right prefrontal repetitive TMS might affect prefrontal mechanisms involved in OCD.	Small case series.
Haghighi M, Shayganfard M, Jahangard L et al. (2015) Repetitive Transcranial Magnetic Stimulation (rTMS) improves symptoms and reduces clinical illness in patients suffering from OCD--Results from a single-blind, randomized clinical trial with sham cross-over condition. Journal of Psychiatric Research 68: 238–44	RCT n=21	Both self- and expert-reported symptom severity reduced in the rTMS condition as compared to the sham condition. Full- and partial responses were seen in the rTMS condition, but not in the sham condition.	Small RCT, included in the systematic review by Rehn et al. (2018).
Hawken ER, Dilkov D, Kaludiev E et al. (2016) Transcranial magnetic stimulation of the supplementary motor area in the treatment of obsessive-compulsive disorder: A multi-site study. International Journal of Molecular Sciences 17: 420	RCT n=22 FU=6 weeks	At the end of the 6 weeks of rTMS, patients in the active group showed a clinically significant decrease in Y-BOCS scores compared to both the baseline and the sham group. This effect was maintained 6 weeks after the end of rTMS treatment. Therefore, in this sample, rTMS appeared to significantly improve the OCD symptoms of the patients who had treatment beyond the treatment window.	Small RCT, included in the systematic review by Rehn et al. (2018).

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Hegde A, Ravi M, Subhasini VS et al. (2016) Repetitive transcranial magnetic stimulation over presupplementary motor area may not be helpful in treatment-refractory obsessive-compulsive disorder: a case series. The Journal of ECT 32: 139–42	Case series n=17	Only 1 patient met the criteria for response after 1 month of treatment initiation. No major adverse effects were seen in any of them.	Small case series.
Jaafari N, Rachid F, Rotge J-Y et al. (2012) Safety and efficacy of repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorder: a review. The World Journal of Biological Psychiatry: the Official Journal of the World Federation of Societies of Biological Psychiatry 13: 164-77	Review	The supplementary motor area and the orbitofrontal cortex appear to be the most promising target areas in terms of potential efficacy. Larger RCTs are needed to better clarify the therapeutic role of rTMS in OCD.	A more recent review with meta-analysis is included.
Jahangard L, Haghighi M, Shyayganfard M et al. (2016) Repetitive transcranial magnetic stimulation improved symptoms of obsessive-compulsive disorder, but also cognitive performance: results from a randomized clinical trial with a cross-over design and sham condition. Neuropsychobiology 73: 224–32	RCT n=10	rTMS is a safe and efficient treatment for patients suffering from refractory OCD; symptoms and cognitive performance improved in parallel.	Small RCT, included in the systematic review by Rehn et al. (2018).
Kang JI, Kim DY, Lee C et al. (2019) Changes of motor cortical excitability and response inhibition in patients with obsessive-compulsive disorder. Journal of Psychiatry & Neuroscience 44: 261–8	Case-control study n=90	Compared to controls, patients with OCD showed a shorter cortical silent period and decreased intracortical facilitation. However, there was no statistically significant difference between groups for resting motor threshold or short-interval intracortical inhibition. In the OCD group, the shortened cortical silent period was associated with a prompt reaction time in the go/no-go task and with early onset of OCD.	Study focuses on motor cortical excitability and response inhibition.
Kang JI, Kim C-H, Namkoong K et al. (2009) A randomized controlled study of sequentially applied repetitive transcranial magnetic stimulation in obsessive-compulsive disorder. The Journal of Clinical Psychiatry 70: 1645–51	RCT n=20	The findings suggest that 10 sessions of sequential rTMS of the right dorsolateral prefrontal cortex and the supplementary motor area at low frequency had no therapeutic effect on obsessive-compulsive symptoms. However, rTMS was a safe method of treatment, and there was no statistically significant change in cognitive function after rTMS. Further controlled studies using a more sophisticated sham system in larger samples are	Small RCT, included in the systematic review by Rehn et al. (2018).

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		needed to confirm the effect of rTMS in OCD.	
Kumar S, Singh S, Chadda RK et al. (2018) The effect of low-frequency repetitive transcranial magnetic stimulation at orbitofrontal cortex in the treatment of patients with medication-refractory obsessive-compulsive disorder. Journal of ECT 34: e16–9	Case series n=25 FU=1 month	Partial response=52% (13/25) Complete response=44% (11/25) Higher number of failed medication trials was statistically significantly associated with a greater chance of non-response to rTMS.	A larger, more recent case series from the same centre is included (Singh et al. 2019).
Kumar N, Chadda RK (2011) Augmentation effect of repetitive transcranial magnetic stimulation over the supplementary motor cortex in treatment refractory patients with obsessive compulsive disorder. Indian Journal of Psychiatry 53: 340–2	Case series n=12	Mean scores on Y-BOCS were 26.17 at baseline and 17.17 at the end of treatment, reflecting a statistically significant improvement. The patients did not report any significant side effects except 1 person with known bipolar illness, who developed manic symptoms after the third session of the rTMS. Low-frequency rTMS over the SMA appears a promising treatment strategy as an add-on treatment for patients with OCD refractory to treatment.	Small case series.
Lee Y-J, Koo B-H, Seo W-S et al. (2017) Repetitive transcranial magnetic stimulation of the supplementary motor area in treatment-resistant obsessive-compulsive disorder: An open-label pilot study. Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia 44: 264–8	Case series n=9	There was a statistically significant reduction in Y-BOCS score at the fourth week of the treatment. Reduction in compulsion contributed to the reduction of global Y-BOCS whereas there was no statistically significant reduction in obsession. Clinical global impression-global improvement also showed a statistically significant change at the second and fourth week of the treatment. No additional statistically significant changes or significant adverse effects were seen.	Small case series.
Lusicic A, Schruers K, Pallanti S et al. (2018) Transcranial magnetic stimulation in the treatment of obsessive-compulsive disorder: current perspectives. Neuropsychiatric Disease and Treatment 14: 1721–36	Systematic review 20 studies	rTMS shows promise as part of a toolbox of current psychiatric treatment options for OCD.	There is no meta-analysis.
Ma ZR, Shi LJ (2014) Repetitive transcranial magnetic stimulation (rTMS) augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant obsessive-compulsive disorder (OCD): a meta-analysis of	Systematic review and meta-analysis 9 studies	Active rTMS was an effective augmentation strategy in treating SSRI-resistant OCD with a pooled weighted mean difference of 3.89 (95% CI 1.27 to 6.50) for reducing Y-BOCS score and a pooled odds	A more recent systematic review is included (Rehn et al. 2018), with

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randomized controlled trials. International Journal of Clinical and Experimental Medicine 7: 4897–905		ratio of 2.65 (95% CI 1.36 to 5.17) for response rates. Further large-scale multicentre RCTs are needed.	most of the same studies.
Ma X, Huang Y, Liao L et al. (2014) A randomized double-blinded sham-controlled trial of alpha electroencephalogram-guided transcranial magnetic stimulation for obsessive-compulsive disorder. Chinese Medical Journal 127: 601–6	RCT n=46 FU=1 week	alphaEEG-guided TMS may be an effective treatment for OCD and related anxiety. Delayed response to alphaTMS in depression suggests that it might be secondary to the improvement of primary response in OCD and anxiety.	Small RCT, included in the systematic review by Rehn et al. (2018).
Mansur CG, Myczkowki ML, de Barros Cabral S et al. (2011) Placebo effect after prefrontal magnetic stimulation in the treatment of resistant obsessive-compulsive disorder: a randomized controlled trial. The International Journal of Neuropsychopharmacology 14: 1389–97	RCT n=30 FU=6 weeks	One patient in each group showed a positive response (p=1.00). For Y-BOCS score, there was a statistically significant effect of time (F=7.33, p=0.002) but no statistically significant group effect or group*time interaction. In treatment-resistant OCD, active rTMS over the rDLPFC does not appear to be superior to sham rTMS in relieving obsessive-compulsive symptoms, reducing clinical severity, or improving treatment response, although there is evidence of a placebo effect.	Small RCT, included in the systematic review by Rehn et al. (2018).
Mantovani A, Rossi S, Bassi BD et al. (2013) Modulation of motor cortex excitability in obsessive-compulsive disorder: an exploratory study on the relations of neurophysiology measures with clinical outcome. Psychiatry Research 210: 1026–32	RCT n=18	Treatment-induced changes in cortical excitability measures are consistent with an inhibitory action of SMA rTMS on dysfunctional motor circuits in OCD. Correlations of neurophysiology measures with therapeutic outcome are supportive of the role of SMA in the modulation of OCD symptoms.	Study focuses on the relationship of neurophysiology measures with clinical outcome.
Mantovani A, Simpson HB, Fallon BA et al. (2010) Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. The International Journal of Neuropsychopharmacology 13: 217–27	RCT n=21	After 4 weeks, the response rate in the completer sample was 67% (6/9) with active and 22% (2/9) with sham rTMS. At 4 weeks, patients having active rTMS showed on average a 25% reduction in the Y-BOCS compared to a 12% reduction in those having sham. In those who had 8-weeks active rTMS, OCD symptoms improved from 28.2+/-5.8 to 14.5+/-3.6.	Small RCT, included in the systematic review by Rehn et al. (2018).
Mantovani A, Lisanby SH Pieraccini F et al. (2006) Repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive-compulsive disorder (OCD) and	Case series n=10	Suggestions of clinical improvement were apparent as early as the first week of rTMS. At the second week of treatment, statistically significant reductions were seen in the Y-BOCS and	Small case series.

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Tourette's syndrome (TS). The International Journal of Neuropsychopharmacology 9: 95–100		other outcome measures. Symptom improvement was correlated with a statistically significant increase of the right resting motor threshold and was stable at 3 months follow up. Slow rTMS to SMA resulted in a significant clinical improvement and a normalisation of the right hemisphere hyperexcitability, thereby restoring hemispheric symmetry in motor threshold.	
Martin JLR, Barbanoj MJ, Perez V et al. (2003) Transcranial magnetic stimulation for the treatment of obsessive-compulsive disorder. The Cochrane database of systematic reviews (no. 3): cd003387	Systematic review 2 studies	It was not possible to pool any results for a meta-analysis. No difference was seen between rTMS and sham TMS using the Y-BOCS or the HAM-D for all time periods analysed.	A more recent systematic review is included (Rehn et al. 2018).
Mendes-Filho VA, de Jesus DR, Belmonte-de-Abreu P et al. (2016) Effects of repetitive transcranial magnetic stimulation over supplementary motor area in patients with schizophrenia with obsessive-compulsive-symptoms: A pilot study. Psychiatry Research 242: 34–8	RCT n=12 FU=4 weeks	rTMS did not statistically significantly change the outcomes after treatment and on the follow up. There seemed to be a trend towards improvement of Brief Psychiatric Rating Scale scores 4 weeks after rTMS treatment compared with sham. No side effects were reported. Future studies with larger sample sizes are needed.	Studies with more patients are included.
Modirrousta M, Shams E, Katz C et al. (2015) The efficacy of deep repetitive transcranial magnetic stimulation over the medial prefrontal cortex in obsessive compulsive disorder: results from an open-label study. Depression and Anxiety 32: 445–50	Case series n=10 FU=1 month	All patients had improvement in their OCD symptoms after 10 sessions of rTMS (mean improvement in Y-BOCS score was 39%; SD=15%; p<0.001). This improvement persisted 1 month following the last session of rTMS.	Small case series.
Nauczyciel C, Le Jeune F, Naudet F et al. (2014) Repetitive transcranial magnetic stimulation over the orbitofrontal cortex for obsessive-compulsive disorder: a double-blind, crossover study. Translational Psychiatry 4: e436	RCT n=19	At day 7, there was a statistically significant decrease from baseline in the Y-BOCS scores, after both active (p<0.01) and sham stimulation (p=0.02). This decrease tended to be larger after active stimulation than after sham stimulation: −6 (−29, 0) points versus −2 (−20, 4) points (p=0.07).	Small RCT, included in the systematic review by Rehn et al. (2018).
Pelissolo, Antoine; Harika-Germaneau, Ghina; Rachid, Fady; et al. (2016) Repetitive transcranial magnetic stimulation to supplementary motor area in refractory obsessive-compulsive disorder treatment: a sham-controlled trial. The International Journal of	RCT n=40	Low-frequency repetitive TMS applied to the presupplementary area seems ineffective for the treatment of OCD patients, at least in severe and drug-refractory cases such as those included in this study.	Small RCT, included in the systematic review by Rehn et al. (2018).

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Neuropsychopharmacology: 19: 1–6			
Prasko J, Paskova B, Zalesky R et al. (2006) The effect of repetitive transcranial magnetic stimulation (rTMS) on symptoms in obsessive compulsive disorder. A randomized, double blind sham controlled study. Neuro Endocrinology Letters 27: 327–32	RCT n=33	Low-frequency rTMS administered over the left dorso-lateral prefrontal cortex during 10 daily sessions did not differ from sham rTMS in facilitating the effect of SSRIs in OCD patients.	Small RCT, included in the systematic review by Rehn et al. (2018).
Rapinesi C, Kotzalidis G, Ferracuti S et al. (2019) Brain stimulation in obsessive-compulsive disorder (OCD): a systematic review. Current Neuropharmacology 7: 787–807	Systematic review 20 studies	Overall, rTMS was found to be a valid alternative to treat OCD that responded poorly to medication, with a quite favourable adverse event profile. Deep TMS could be a step forward in the direction of non-invasive techniques to supplement current treatment approaches. The issue of whether to adopt high or low frequencies and which brain region to target with rTMS is still unresolved.	No meta-analysis was done because of study heterogeneity.
Ruffini C, Locatelli M, Lucca A et al. (2009) Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: a controlled investigation. Primary Care Companion to the Journal of Clinical Psychiatry 11: 226–30	RCT n=23 FU=12 weeks	There was a statistically significant reduction of Y-BOCS scores comparing active with sham treatment for 10 weeks after the end of rTMS ($p<0.02$), with loss of significance after 12 weeks ($p<0.06$).	Small RCT, included in the systematic review by Rehn et al. (2018).
Sachdev PS, Loo CK, Mitchell PB et al. (2007) Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double-blind controlled investigation. Psychological Medicine 37: 1645–9	RCT n=18	The 2 groups did not differ on change in Y-BOCS or Maudsley Obsessive-Compulsive Inventory scores over 10 sessions, with or without correction for depression ratings. Over 20 sessions, there was a statistically significant reduction in total Y-BOCS scores, but not after controlling for depression. rTMS over 20 sessions was well tolerated.	Small RCT, included in the systematic review by Rehn et al. (2018).
Sachdev PS, McBride R, Loo CK et al. (2001) Right versus left prefrontal transcranial magnetic stimulation for obsessive-compulsive disorder: a preliminary investigation. The Journal of Clinical Psychiatry 62: 981–4	RCT n=12	A proportion (about one quarter) of patients had resistant OCD that appeared to respond to rTMS to either prefrontal lobe, although a placebo response cannot be ruled out.	Studies with more patients are included.
Sarkhel S, Sinha VK, Praharaj SK (2010) Adjunctive high-frequency right prefrontal repetitive transcranial magnetic stimulation (rTMS) was not effective in obsessive-compulsive disorder but improved secondary depression.	RCT n=42	Adjunctive high-frequency right prefrontal rTMS does not have any significant effect in the treatment of OCD. However, it is modestly effective in the treatment of comorbid depressive symptoms in patients with OCD.	Small RCT, included in the systematic review by Rehn et al. (2018).

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Journal of Anxiety Disorders 24: 535–9			
Seo H-J, Jung Y-E, Lim HK et al. (2016) Adjunctive low-frequency repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex in patients with treatment-resistant obsessive-compulsive disorder: A randomized controlled trial. Clinical Psychopharmacology and Neuroscience 14: 153–60	RCT n=27	Low-frequency rTMS over the right DLPFC appeared to be superior to sham rTMS for relieving OCD symptoms and depression in patients with treatment-resistant OCD. Further trials with larger sample sizes should be conducted to confirm the present findings.	Small RCT, included in the systematic review by Rehn et al. (2018).
Shayganfard M, Jahangard L, Nazaribadie M et al. (2016) Repetitive transcranial magnetic stimulation improved symptoms of obsessive-compulsive disorders but not executive functions: results from a randomized clinical trial with crossover design and sham condition. Neuropsychobiology 74: 115–24	RCT n=10	Whereas the present study confirmed previous research suggesting that rTMS improved symptoms of OCD, rTMS did not improve executive functions to a greater degree than sham treatment. More research is needed to investigate the effect of rTMS on executive functions in patients with OCD.	Studies with more patients are included.
Shivakumar V, Dinakaran D, Narayanaswamy J et al. (2019) Noninvasive brain stimulation in obsessive-compulsive disorder. Indian Journal of Psychiatry 61: 66–s76	Review	TMS studies that administered inhibitory rTMS over OFC reported consistently positive effects on symptom reduction. However, those studies are few in number and sample size was less when compared against other areas in a meta-analysis. Studies involving SMA and DLPFC areas reported mixed results, and all the findings from those studies are limited by small sample sizes. Various researchers have attempted pooling data from the above studies to overcome this limitation by conducting meta-analyses. All 5 meta-analyses uniformly suggested that there is definite benefit of add-on true rTMS in patients with resistant OCD. Recent studies have suggested that low-frequency/high-frequency stimulation of SMA area and DLPFC area are beneficial. Most of the studies were conducted on resistant OCD patients and for a shorter duration of time ranging from 1 to maximum 12 weeks.	No meta-analysis.
Tan O, Hizli SG, Onen UB et al. (2015) Combining transcranial magnetic stimulation and cognitive behavioral therapy in treatment resistant obsessive-compulsive	Case series n=18	The combination of pharmacotherapy, CBT and rTMS may be effective in treatment-resistant and chronic OCD in the short term.	Small case series.

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disorder. Anadolu Psikiyatri Dergisi 16: 180–8			
Trevisol A, Shiozawa P, Cook I et al. (2016) Transcranial magnetic stimulation for obsessive-compulsive disorder. An updated systematic review and meta-analysis. Journal of ECT 32: 262–66	Systematic review and meta-analysis 15 studies	TMS was superior to sham stimulation for ameliorating OCD symptoms. Further RCTs with larger sample sizes are needed to clarify the precise impact of TMS on OCD symptoms.	A more recent systematic review is included (Rehn et al. 2018), with most of the same studies.
Zaman R, Robbins TW (2017) Is there potential for Repetitive Transcranial Magnetic Stimulation (RTMS) as a treatment of OCD? Psychiatria Danubina 29: 672–s678	Review	Published research so far points towards rTMS as potentially a valuable treatment tool for OCD. Large and better designed multicentre studies, with some standardisation of rTMS protocols and utilising some of the newer techniques, in combination with imaging tools will not only give a better understanding of the precise cortical targets for rTMS, but are also likely to address the question definitively, whether rTMS should be part of treatment protocol for OCD along with SSRIs and CBT.	A more recent systematic review is included (Rehn et al. 2018).
Zhou D-D, Wang W, Wang G-M et al. (2017) An updated meta-analysis: Short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder. Journal of Affective Disorders 215: 187–96	Systematic review and meta-analysis 20 studies	Based on this study, the short-term therapeutic effects of rTMS are superior to those of sham treatments. The site of stimulation, stimulation frequency and intensity and sham condition were identified as potential factors modulating short-term therapeutic effects.	A more recent systematic review is included (Rehn et al. 2018).

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