EUnetHTA Joint Action 3 WP4

Rapid assessment of other technologies using the HTA Core Model® for Rapid Relative Effectiveness Assessment

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION FOR TREATMENT-RESISTANT MAJOR DEPRESSION

Project ID: OTCA05

Version 4, 30 March 2017

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description
V1.0	**24/02/17**	First draft.
V1.1	**27/02/17**	Input from co-author has been processed.
V1.2	**09/03/17**	Input from dedicated reviewers has been processed.
V1.3	**22/03/17**	Input from external experts and manufacturer(s) has been processed.
V1.4	**23/03/17**	Input from medical editor has been processed.

Disclaimer

The assessment represents a consolidated view of the EUnetHTA network members and is in no case the official opinion of the participating institutions or individuals. EUnetHTA Joint Action 3 is supported by a grant from the European Commission. The sole responsibility for the content of this document lies with the authors and neither the European Commission nor EUnetHTA are responsible for any use that may be made of the information contained therein.

Assessment team

Author(s)	Ludwig Boltzmann Institute for Health Technology Assessment, Austria (LBI-HTA)
Co-Author(s)	Basque Office for Health Technology Assessment (OSTEBA)
Dedicated Reviewer(s)	Belgian Health Care Knowledge Centre (KCE), Fundación Canaria de Investigación Sanitaria (FUNCANIS)

Further contributors

Consultation of the draft Rapid Assessment

Manufacturer(s) v1.2	Neurosoft, Russia Mag&More, Germany (factual accuracy check)
External experts v1.2	Dr. Emmanuel Haffen, Professor of psychiatry, President of French Association of Biological Psychiatry and Neuropsychopharmacology, Head of laboratory of Neurosciences of the University of Franche-Comté, Head of the Clinical Investigation Centre of the University hospital of Besançon Dr. Jose Mª Vergara Ugarriza, Head of Neurophysiology of Miguel Servet University Hospital (Zaragoza), Aragon
Proof reading v1.3	Michal Stanak, Ludwig Boltzmann Institute for Health Technology Assessment, Austria

Conflict of interest

All authors and reviewers involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology assessed according to the EUnetHTA Declaration of interest and confidentiality undertaking of interest (DOICU) statement form.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

Tables

Figures

LIST OF ABBREVIATIONS

ACROBAT-NRSi	A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions
ADE	Adverse device effect
AE	Adverse event
AGREE II	Advancing guideline development reporting and evaluation in healthcare
AMSTAR	A Measurement Tool to Assess Systematic Reviews
AOTMiT	Agencja Oceny Technologii Medycznych i Taryfikacji/Agency for Health Technology Assessment and pricing
APA	American Psychiatric Association
aTMS	Accelerated repetitive transcranial magnetic stimulation
AVALIA-t	Galician Agency for Health Technology Assessment
B	bilateral
BDI	Beck Depression Inventory
B-rTMS	Bilateral repetitive transcranial magnetic stimulation
C	Control
CANMAT	Canadian Network for Mood and Anxiety Treatments
CBR	Consensus based recommendation
CE mark	Conformité Européene
CHIF	Croatian Health Insurance Fund
CI	Confidence interval
CPG	Clinical practice guideline
CRD	Centre for Research and Dissemination
CST	Color Stroop Test
DBS	Deep brain stimulation
DGPPN	Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde/German Association for Psychiatry and Psychotherapy
DLPFC	Dorsolateral prefrontal cortex
DRG	diagnosis-related group
DSM IV-TR	Diagnostic and statistical manual of mental disorders IV text revision
DTMS	Deep transcranial magnetic stimulation
EBR	Evidence-based recommendations
ECT	Electroconvulsive therapy
EEG	Electromyography
ETH	Ethical
EUnetHTA	European Network of Health Technology Assessment
FDA	Food and Drug Administration
fMRI	Functional magnetic resonance imaging
FU	Follow-up

G-BA	Gemeinsamer Bundesausschuss
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	French National Authority for Health
H-coil	Hesed-coil
HDRS/HAMD	Hamilton Depression Rating Scale
HF	High-frequency
HQO	Health Quality Ontario
HTA	Health Technology Assessment
Hz	Hertz
I	Intervention
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
IFCN	International Federation of Clinical Neurophysiology
INFARMED	National Authority of Medicines and Health Products
LBI-HTA	Ludwig Boltzmann Institute for Health Technology Assessment
LEG	Legal
LF	Low-frequency
MA	Meta-analysis
MADRS	Montgomery-Asberg Depression Rating Scale
MAOB	Monoamine oxidase B
MAOI	Monoamine oxidase inhibitors
MDD	Major depressive disorder
MDE	Major depressive episode
MEP	Muscular-evoked potential
MeSH	Medical Subject Headings
MMSE	Mini-Mental State Examination
mo	month
MST	Magnetic seizure therapy
MT	Motor threshold
n	number
N/A	not available
NAMI	National Alliance on Mental Illness
NARSAD	National Alliance for Research on Schizophrenia and Depression
NCCHTA	National Coordinating Centre for Health Technology Assessment
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHM	National Institute of Mental Health
NIJZ	National Institute of Public Health Slovenia

NIRS	Near Infrared Spectroscopy
NOS	Not Otherwise Specified
OGYEI	Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet/National Institute of Pharmacy and Health Products
ORG	Organizational
OSTEBA	Basque Office for Health Technology Assessment
PCP	Phencyclidine
PET	Positron emission tomography
pts	patients
QIDS	Quick Inventory of Depressive Symptomatology
Q-LES-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
QoL	Quality of life
RAZCP	Royal Australian and New Zealand College of Psychiatrists
RCT	Randomized controlled trial
REA	Relative Effectiveness Assessment
RedAETS	Red Española de Agencias de Evaluación de Tecnologías Sanitarias
RMT	Resting motor threshold
RR	Relative risk
R-rTMS	Right-side repetitive transcranial magnetic stimulation
rTMS	Repetitive transcranial magnetic stimulation
SADE	Serious adverse device effect
SCID	Structured Clinical Interview for DSM-IV
SD	Standard deviation
SESCS	Evaluation Unit of the Canary Islands Health Service
SF 36 PF	Short Form (36) Health Survey Physical Functioning
SF-36	Study-36 Item Short Form
SIGH-SAD	Structured Interview Guide for the Hamilton Depression Rating Scale
SIGN	Scottish Intercollegiate Guidelines Network
SMD	Standardized mean difference
SNRI	Serotonin–norepinephrine reuptake inhibitors
SOC	Social
SR	Systematic review
SSES	Suicide severity rating scale
SSRI	Selective serotonin reuptake inhibitors
STAI	State-Trait Anxiety Inventory
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
sTMS	Synchronized transcranial magnetic stimulation
TBS	Theta Burst Stimulation
TCA	Tricyclic antidepressants

TDCS	Transcranial direct current stimulation
TGA	Therapeutic Goods Administration
TMS	Transcranial magnetic stimulation
TMT	Trail Making Test
TRD	Treatment-resistant depression
UK	United Kingdom
UMDNS	Universal Medical Device Nomenclature System
VFT	Verbal Fluency Test
VNS	Vagus nerve stimulation
vs	versus
w	week
WCST	Wisconsin Card Sorting Test
WHO	World Health Organization
WSFBP	World Federation of Societies of Biological Psychiatry
Yrs	Years

SUMMARY OF RELATIVE EFFECTIVENESS OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Scope

The scope can be found here: Scope. The aim of this report was to assess the effectiveness and safety of repetitive transcranial magnetic stimulation (rTMS) in treatment-resistant depression (TRD).

Introduction

Description of technology

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neurostimulation and neuromodulation technique that is delivered as a series of pulses i.e. a train. The most typical technical parameters of rTMS are the frequency (high-frequency: stimulation delivered >1 pulse per second, but generally ≥ 5 Hz is applied as HF [1, 2], or low-frequency: stimulation delivered at ≤ 1 pulse per second), intensity (expressed as a percentage of the resting motor threshold generally set at 100-120%), train duration, intertrain interval, number of trains per session, and number of pulses per session [2, 3].

There are various treatment protocols, but the FDA-based standard parameters are most widely used and for the acute treatment, they include: 10 magnetic pulses per second (Hz), 3.000 pulses per session, 100 to 120 percent of motor threshold, train duration of 4 s with intertrain interval of 26 s [4]. However, the stimulation parameters required to optimize the efficacy of rTMS treatment are not well known.

The use of rTMS is prohibited for patients with metal implants in the head area, implanted medical devices (cochlear implant, medication pump, pacemaker, intra-cardiac lines, etc.), increased intracranial pressure, a history of epileptic seizures, increased cerebral susceptibility to epileptic seizures through medication, unstable general medical disorders, and during pregnancy [2, 3, 5] (**B0001**).

rTMS is indicated for patients with unipolar major depression who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode (**A0020**). The claimed benefit of rTMS is that it is non-invasive, the patient remains awake and alert throughout the process, no post-session recovery is needed, the patient can resume normal activities immediately, and no cognitive side-effects have been reported with rTMS.

Comparators

Sham stimulation is delivered with a sham coil.

Electroconvulsive therapy (ECT) involves the induction of a seizure by the application of electrical current to the brain. It is delivered under general anaesthesia and application of a muscle relaxant. Treatment parameters include electrode position, electrical intensity, pulse width, and duration. The most common electrode placements are bilateral or right unilateral. The electrical intensity is based on the minimum intensity to produce a generalized seizure, called the seizure threshold. [6]. ECT is a complex intervention and its efficacy and safety are affected by a number of parameters including the placement of electrodes, dosage and waveform of the electrical stimulus, and the frequency with which ECT is administered [7]. As regards to mortality, ECT is a safe procedure

with a very low mortality rate (1 death per 73.440 treatments), approximating the risk of general anaesthesia [6] (**B0001**). However, cognitive effects including transient disorientation when recovering from ECT sessions, retrograde amnesia, anterograde amnesia, mild, short-term, impairment in memory, and other cognitive domains during and after the treatment with ECT might occur. Nevertheless, these impairments are normally transient and the cognitive functioning recovers within weeks or months after the acute course of ECT [6, 8] (**B0002**).

Health problem

The target condition in the scope of the assessment is treatment-resistant major depressive disorder (TRD), which often refers to major depressive disorder (MDD) that does not respond satisfactorily to at least two trials of antidepressant monotherapy. However, the definition has not been standardized yet. Defining treatment resistant depression is also complicated due to the lack of consensus in describing acute antidepressant responses. In many studies, response is classified as ≥ 50 percent improvement from baseline on the depression rating scale. Remission is defined as a depression rating scale score less than or equal to a specific cut-off that defines the normal range (score on the HRSD-17 or on the MASD ≤ 7) [9] (**A0002**).

The prevalence of unipolar TRD is not clear due to the lack of internationally acknowledged and standardized definition. However, there are reasonable estimates available. MDD is the fourth leading cause of disability and is predicted to be the second most disabling disease across all countries by 2020 [10]. If response is used as outcome, according to the definition of response, the prevalence rate for Stage 2 TRD (failure to achieve response after two courses of adequate treatment) is estimated to be 15-35% [1, 11, 12] (**A0023**).

MDD is currently diagnosed by using the Diagnostic Criteria for Major Depressive Disorder and Depressive Episodes (DSM-IV-TR) (details in Appendix 4). Because of differences in treatment, the diagnosis of unipolar MDD should be confirmed and other diagnosis such as bipolar depression or dysthymic disorder ruled out. The treatment history of patients who may be treatment resistant is usually assessed through a clinical interview as well as a review of the medical record [9] (**A0024**).

Methods

The systematic literature search and analysis of the studies was performed in two phases: secondary studies (i.e. HTA reports and systematic reviews/SRs) were screened as a first step and evaluated on the basis of their scope, inclusion and exclusion criteria, and quality. Primary studies were considered for inclusion in the second step. The AMSTAR tool was used for quality assessment of SRs. The Health Quality Ontario (HQO) report [13] was selected for update.

As a second step, to identify further, more recent, primary studies fulfilling the inclusion criteria of the present assessment, a literature search for randomized controlled trials (RCTs) published since the literature search of the chosen HQO report [13] was performed. 2 studies [14, 15] were selected that fulfilled our inclusion criteria and are included within the present assessment. The 2 studies compare HF-rTMS to the left DLPFC with sham. No studies were found that compared active stimulation with ECT. The Cochrane risk of bias assessment approach was used to assess RCTs. For the assessment of the strength of evidence, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [16] approach was used.

Results

Available evidence

rTMS vs sham

23 studies met the inclusion criteria in the HQO report. We found additional two RCTs [14, 15] that met our inclusion criteria and are included in the present analysis. One of them [15] is the 6 month follow-up of a study included in the HQO report [17]. A total of 1,180 patients were analysed in the studies, 615 in the rTMS arm and 565 in the sham arm.

The inclusion criteria of the studies varied as follows:

- Baseline values on HDRS-17
  - In 11 studies: >25 (severe depression)
  - In 6 studies: 19-24 (moderate depression)
- TRD definition
  - In 16 studies: two or more failed antidepressant trials
  - In 9 studies: one or more failed antidepressant trial
- rTMS as add-on or monotherapy
  - In 17 studies: add-on therapy
  - In 8 studies: monotherapy

The stimulation parameters also varied: the frequency ranged from 5 to 20 Hz, the intensity from 80 to 120% of patients' MT, the number of trains per session from 15 to 75, the train duration from 2 to 10 seconds (s), the intertrain interval from 22 to 58 s, the number of pulses per session from 800 to 3,000, and the total number of pulses during rTMS treatment from 8,000 to 90,000. All studies used the figure 8 coil.

rTMS vs ECT

The HQO report [13] included six studies that compared rTMS with ECT. Most of the studies were conducted in the early 2000s. The total number of patients was 266, 133 in each arm. Two of the studies reported 6 month follow-up data as well [18, 19].

The inclusion criteria of the studies varied as follows:

- Baseline values on HDRS-17
  - In the rTMS group: 24-26
  - In the ECT group: 25-28
- TRD definition
  - In 2 studies: two or more failed antidepressant trials
  - In 1 study: one or more failed antidepressant trial
  - In 2 studies the number of failed antidepressant trials was not reported, only the number of failed ECT trials

The characteristics of the intervention varied also, one study used 20 Hz frequency stimulation, four studies used 10 Hz, and the last study did not report on the frequency used. The intensity of the stimulation ranged from 90 to 110% of the MT, the number of trains from 20 to 30-35, the train duration from 2 to 10 s, the intertrain interval from 20 to 55 s, the pulses per session from 408 to 2500, and the number of sessions from 10 to 20. Hence, the total number of pulses delivered also ranged from 4,080 to 50,000. All studies reported that they used the figure 8 coil.

Clinical effectiveness

rTMS vs sham

The pooled risk ratio for response rate across 19 studies was 1.82 (95% CI 1.18-2.82, p=.0068). There was a moderate degree of heterogeneity among studies (I^2=50%, p=.01). This pooled estimate suggests that patients may be twice more likely to experience treatment response with rTMS than with sham. The pooled risk ratio for remission rate across 12 studies was 2.16 (95% CI 1.42-3.29, p=.0003). No heterogeneity was observed among the studies (I2=0.0%, p=.7164). This pooled estimate suggests that patients may be twice more likely to experience remission with rTMS than with sham. On average, rTMS reduced depression scores by about 2.31 points more than sham (95% CI 1.19-3.43), p<.001), which is below the mean value that was deemed a priori as clinically important (threshold of 3.5 points).

One RCT [15] described QoL outcomes from acute treatment with rTMS. There was a statistically significant improvement favoring rTMS on the general health and mental health SF-36 subscales at 4- and 6-weekfollow-up. Statistically significant improvement favoring rTMS was also seen in the Q-LES-Q total score at 4-and 6-week follow-up. (**D0012**, **D0013**).

rTMS vs ECT

The pooled risk ratio for response at the end of treatment was 1.72 (95% CI 0.95-3.11, p=.072) favoring ECT. There was again a high degree of heterogeneity among studies (I^2=60.6%, p=.079). While the effect is not statistically significant, this pooled estimate would suggest a higher response with ECT than with rTMS

The pooled risk ratio for remission was 1.44 (95% CI 0.64-3.23, p=.375) at the end of treatment, favoring ECT. However, these results are not significant. There was a high degree of heterogeneity among studies (I^2=69.1%, p=.039) (**D0006**).

The weighted mean difference of depression scores from baseline to the end of treatment was -5.97 points (95% CI -11.0 to -0.94, p=.020) in favour of ECT, which is higher than the mean value that was defined a priori as clinically important. The degree of heterogeneity among studies was high (I^2=72.2%, p=.013) (**D0005**).

One study [20] reported data on suicide scores or suicidal ideations. The suicide score decreased from 1.5 (0.8) to 1.2 (0.9) as measured by BDI and from 1.9 (1.3) to 1.4 (1.2) as measured by HDRS in the rTMS group. In the ECT group, the decrease was significantly greater: from baseline 1.4 (1.0) to 0.5 (0.7) as measured by BDI and 2.3 (1.1) to 0.3 (0.5) as measured by HDRS (p<.001). The results suggest that ECT decreases suicidal scores more than rTMS.

Safety

rTMs vs sham

The most common side-effect presented in the studies was headache. The rate of headache ranged from 0 to 60% in the rTMS group and 0 to 50% in the sham group. Seizures did not occur in any of the studies, transient impairment of working memory occurred in five patients (16.7%) in the rTMS group and in one patient (4.3%) in the sham group (**C0008**).

rTMS vs ECT

No serious safety concerns were identified. The most common side-effects were headaches in rTMS-treated patients. No adverse events occurred in ECT-treated patients (**C0008**).

Upcoming evidence

There are four ongoing studies on rTMS compared to sham stimulation, no ongoing studies comparing rTMS with ECT.

Reimbursement

The technology is not reimbursed in the majority of countries for which we have information available (**A0021**). The reason for its non-inclusion in the benefit catalogue is either that it has not been assessed or that the evidence is insufficient to issue a recommendation.

Table 1: Summary table of relative effectiveness of rTMS

Treatment resistant depression					
	Health benefit			Harm	
	Standardized mean difference in depression scores	Response rate	Remission rate	Transient impairment in working memory	Seizures
rTMS vs sham	**MD 2.31** (95% CI 1.19 to 3.43)	**RR 1.82** (95% CI 1.18 to 2.82) **Absolute effect 99 more per 1000** (95% CI 22 more to 219 more) **Risk difference 0.13** (95% CI 0.09 to 0.17)	**RR 2.16** (95% CI 1.42 to 3.29) **Absolute effect 82 more per 1000** (95% CI 30 more to 162 more) **Risk difference 0.10** (95% CI 0.08 to 0.14)	**RR 3.83** (95% CI 0.48 to 30.59) **Absolute effect 123 more per 1000** (95% CI 23 fewer to 1,000 more)	**RR 0.84** (95% CI 0.01 to 42.01) **Absolute effect 0 fewer per 1000** (95% CI from 0 fewer to 0 fewer)
Assessment elements	**D0005**	**D0006**	**D0006**	**C0008**	**C0008**
Quality of body of evidence[+]	**Moderate**	**Very low**	**Low**	**Very low**	**Low**
rTMS vs ECT	**MD -5.97** (95% CI -11.00 to -0.94)	**RR 1.72** (95% CI 0.95 to 3.11) **Absolute effect 270 more per 1000** (95% CI from 19 fewer to 791 more)	**RR 1.44** (95% CI 0.64 to 3.23) **Absolute effect 154 more per 1000** (95% CI from 126 fewer to 781 more)	**RR 1.13** (95% CI 0.02 to 55.96) **Absolute effect 0 fewer per 1000** (95% CI from 0 fewer to 0 fewer)	**RR 3.39** (95% CI 0.14 to 81.46) **Absolute effect 45 more per 1000** (95% CI from 16 fewer to 1,000 more)
Assessment elements	**D0005**	**D0006**	**D0006**	**C0008**	**C0008**
Quality of body of evidence[+]	**Very low**	**Very low**	**Very low**	**Low**	**Low**

Abbreviations: CI confidence interval, ECT electroconvulsive therapy, MD mean difference, RR risk ratio, rTMS repetitive transcranial magnetic stimulation

[+] GRADE, High = We are very confident that the true effect lies close to that of the estimate of the effect;
Moderate = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
Low = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Discussion

The overall quality of the body of evidence is very low for both sham and ECT comparison studies.

The methodological limitations of the studies included in this assessment are likely to influencethe robustness of our findings These limitations include variable study parameters (rTMS treatment protocols, the definition of remission, the level of treatment resistance, and if rTMS was used as mono- or add-on therapy), risk of bias (high risk of bias in the blinding domain in ECT controlled studies), small sample sizes (in both the sham and ECT controlled trials).

Ideally, outcomes such as quality of life and function would be primary outcomes that determine the impact of the intervention, but this was not reported in the included studies, except for one. A major limitation in the outcomes is that they are not measuring directly the improvement in the patients' quality of life and that there is only short-term data available. Patient satisfaction was also not measured by any dedicated tool.

Conclusion

The body of evidence indicates that rTMS is generally safe and well-tolerated. rTMS had a small short-term effect for improving depression in comparison with sham, but follow-up studies did not show that the small effect will continue for longer periods. The current evidence is not sufficient to prove if rTMS is as effective and safe as ECT, since no significant differences in remission and response rates were found, and studies showed high heterogeneity at a low total sample size. However, rTMS patients had less, and not clinically relevant decreases in depression scores as compared to ECT patients. No serious safety concerns were observed.

Due to the low quality of evidence, new study results would potentially influence the effect estimate considerably. Additional research is needed to support the findings with high-quality evidence.

1 SCOPE

Description	Project scope

Population	• Adult patients (>18 yrs) with major depressive disorder (MDD) as defined by DSM IV-TR or ICD-10, which is treatment resistant (TRD) and characterized by:
	  ○ syndrome of unipolar depression with or without psychotic features and
	  ○ lack of clinically meaningful improvement despite the use of at least 2 antidepressant agents from different pharmacological classes with each antidepressant medication trial being adequate in terms of dose, duration, compliance, and tolerability
	• Intended use of technology: third- and subsequent-line treatment
	• MeSH terms: Major depressive disorder F03.600.300.375, Depressive disorder, treatment-resistant: F03.600.300.387
	• ICD-10 categories: F32 Depressive episode, F33 Recurrent depressive disorder
	Rationale: population has been chosen based on information from the relevant published clinical guidelines [1, 2, 21-25] and amended following comments from external experts.

Intervention	• Repetitive transcranial magnetic stimulation (rTMS) as a therapeutic intervention in the acute phase
	• MeSH term: Transcranial Magnetic Stimulation E02.621.820
	• The following intervention will be considered:
	• **High-frequency** (≥5 Hz) rTMS **of the left dorsolateral prefrontal cortex** (DLPFC) as *monotherapy* or *add-on therapy*
	• Products to be considered:
	  ○ MagStim: Magstim Rapid2, Super Rapid2 and Super Rapid2 Plus1
	  ○ Magventure: MagVita TMS Therapy system, Magpro X100 Stimulator, Magpro R30 Stimulator
	  ○ Neurostar: NeuroStar TMS therapy system
	  ○ Mag & More: PowerMAG, Different versions: PowerMAG Clinical 30, PowerMAG Clinical 100, PowerMAG Research 30, PowerMAG Research 100
	  ○ Neurosoft: Neuro-MS, Neuro-MS/D
	Rationale: relevant published clinical guidelines [1, 22] issued level A recommendation for the use of high-frequency rTMS of the left DLPFC, for the use of low-frequency rTMS of the right DLPFC level B recommendation (probable effect) has been issued.

Comparison	• **Sham** stimulation (with antidepressant medication or no medication) • **ECT** Rationale: Comparator has been chosen based on information from EUnetHTA guidelines [26-28] and relevant published clinical guidelines [1, 2, 21-25], in which ECT is recommended for TRD patients after two treatment failures as a nonpharmacological treatment option. Other somatic therapies are not yet well established.

Description	Project scope

Outcomes	**Clinical endpoints**
	Clinical effectiveness:
	• Change in depression score (measured on one of the following scales: HDRS/HAMD, MADRS, BDI or QIDS)
	• Response rate (≥ 50% reduction in the depression scores)
	• Remission rate (HAMD score <7, MADRS score <7, QUIDS score <5)
	• Patient satisfaction
	• QoL
	• Relapse rate
	Safety:
	• Serious adverse device effect (SADE)
	  ○ Seizure
	  ○ Transient impairment of working memory
	  ○ Induced currents in implanted devices
	• Adverse device effect (ADE):
	  ○ Syncope (fainting)
	  ○ Scalp discomfort or pain
	  ○ Transient induction of hypomania
	  ○ Transient hearing loss
	  ○ Headache
	  ○ Facial twitching
	  ○ Vertigo
	  ○ Device-related insomnia/drowsiness
	  ○ Mild confusion
	  ○ Other AEs
	Rationale: outcomes have been chosen based on information from relevant published clinical guidelines [1, 2, 21-25] and EUnetHTA guidelines [26-28].

Abbreviations: AEs adverse events, BDI Beck Depression Inventory, HDRS/HAMD Hamilton Depression Rating Scale, MADRS Montgomery-Asberg Depression Rating Scale, QIDS Quick Inventory of Depressive Symptomatolog, QoL quality of life

2 METHODS AND EVIDENCE INCLUDED

2.1 Assessment Team

Description of the distribution of responsibilities and the workload between authors and co-authors:

LBI-HTA (1st author):

- Develop first draft of EUnetHTA project plan, amend the project plan following co-authors', dedicated reviewers', as well as external experts' comments.
- Perform the literature search, screening, and selection, data extraction and risk of bias assessment of the selected references, check the discrepancies with the co-author and reach a consensus.
- Answer assessment elements; fill in the checklist regarding potential ETH, ORG, SOC, LEG aspects of the HTA Core Model® for Rapid Relative Effectiveness (REA).
- Send draft versions to reviewers, compile feedback from reviewers and perform changes according to reviewers' comments.
- Prepare the final assessment and write the executive summary of the assessment.

OSTEBA (co-authors):

- Review and comment on the draft EUnetHTA project plan.
- Check and approve all steps (e.g. literature screening and selection, data extraction, risk of bias assessment).
- Produce the overview of available guidelines and assess their quality.
- Review the draft assessment, propose amendments where necessary (perform additional handsearch of literature if needed) and provide written feedback.

2.2 Source of assessment elements

The selection of assessment elements is based on the HTA Core Model Application for Rapid REA Assessments (4.2). The selected issues (generic questions) are translated into actual research questions (answerable questions).

2.3 Search

Detailed tables on search strategy are included in Appendix 1.

Given the extensive body of evidence (randomized controlled trials/RCTs, systematic reviews/SRs and meta-analysis/MAs) the systematic literature search and analysis of the studies was performed in two phases: secondary studies (i.e. HTA reports and SRs) were screened as a first step and evaluated on the basis of their scope, inclusion and exclusion criteria and quality. Primary studies were considered for inclusion in the second step. We did not apply any restrictions on language.

The following sources of information were used in the first search:

- Cochrane Library,
- Centre for Research and Dissemination (CRD),
- Embase,
- Medline,
- PsychInfo,
- Handsearch (in reference list of relevant studies).

Secondary studies were retrieved in full-text version. HTA reports and SRs were extracted and tabulated in ascending chronological order. Only the most recent reports (published in 2012-2016) were discussed qualitatively. Systematic reviews were assessed according to year of publication, time range, scope, and population to identify the most recent review that overlapped with the scope of the present assessment. The AMSTAR tool was used for quality assessment of systematic reviews. Details can be found in Table A 3 and Table A 4 in Appendix 1. The Health Quality Ontario HTA report [13] was selected for update.

To identify further, more recent, primary studies fulfilling the inclusion criteria of the present assessment a literature search for RCTs published since the literature search of the chosen HTA report [13] was performed. Therefore, the time period of the search was limited to November 2014 to January 2017. The following sources of information were used:

- Cochrane Library,
- Embase,
- Medline,
- PsychInfo,
- Handsearch (in reference list of relevant studies)

In addition, the following clinical trials databases were searched to identify ongoing studies on the rTMS in major depression:

- ClincalTrials.gov
- EU Clinical Trials Register
- International Clinical Trials Registry Platform (ICTRP).

Clinical Practice Guidelines (CPG) were also searched in the UptoDate database, through handsearch and consultation with clinical experts.

2.4 Study selection

1. Selection of systematic reviews

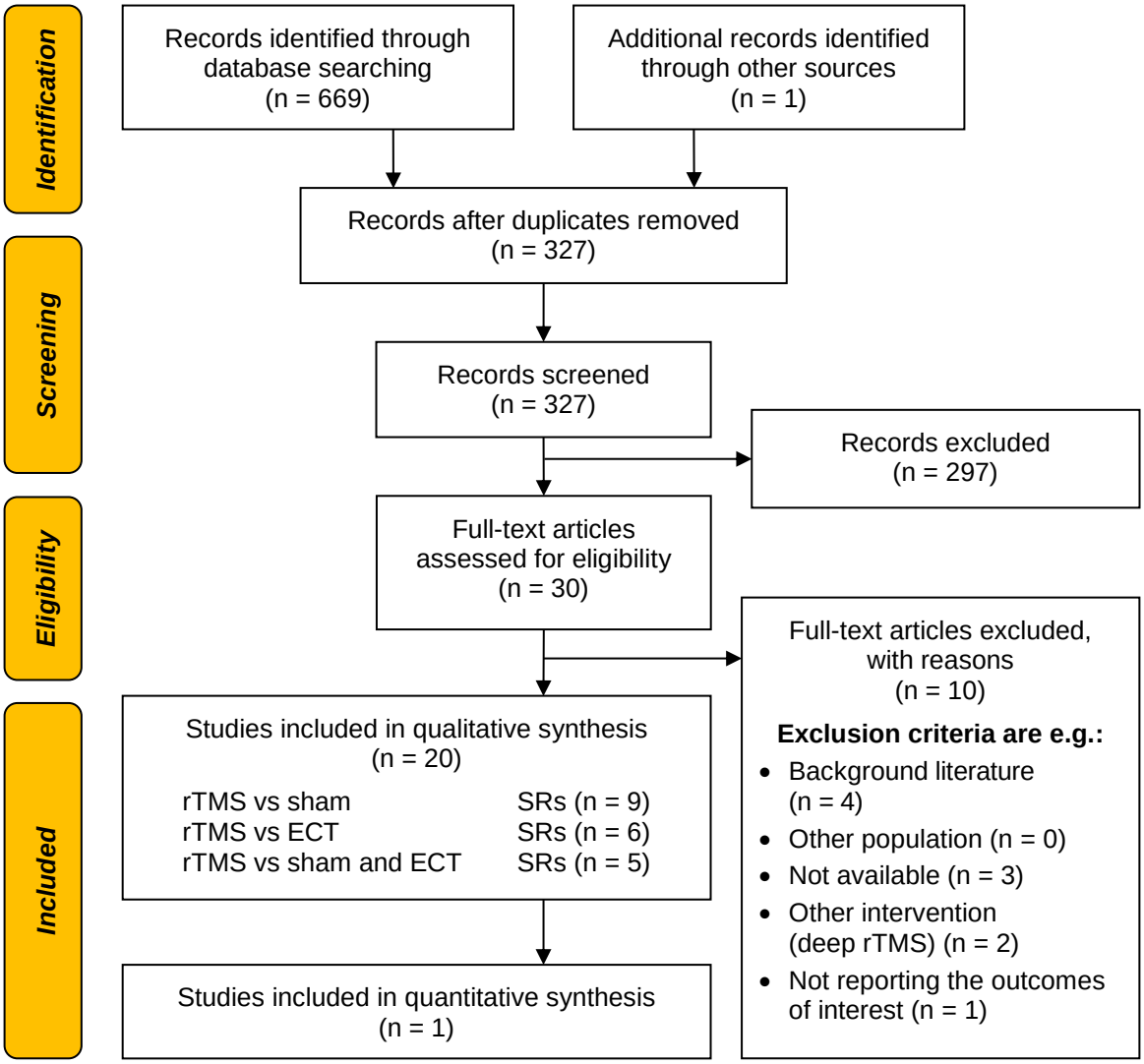

Figure 1: Flow chart for selection of systematic reviews

The author (LBI-HTA) and the co-author (OSTEBA) screened and selected studies independently from each other. The author checked the discrepancies. Any disagreements were resolved by consensus.

The search yielded 669 records and after deduplication 326 records remained for screening. The reference list was screened by title and abstract to identify potentially relevant studies. A cross-reference search identified one further study.

A total of 20 SRs were selected that fulfilled our inclusion criteria. 14 studies had only one comparator each: nine compared rTMS with sham stimulation and six compared active stimulation with ECT. Five SRs included both comparators. Seven SRs included different types of rTMS (HF, LF, mixed frequencies) to different sites. From these we considered only the HF-rTMS to the left DLPFC parts of the SR and extracted data regarding that (number of patients, studies included, scope of the assessment, inclusion criteria used). We assessed the quality of the SRs with the AMSTAR tool. The Health Quality Ontario report [13] was selected for update within the present

assessment on the basis of the year of publication, time range, scope, population, intervention, outcomes measured, comparators and the AMSTAR score. Primary studies in the period November 2014 – January 2017 were screened to identify new evidence.

2. Selection of primary studies

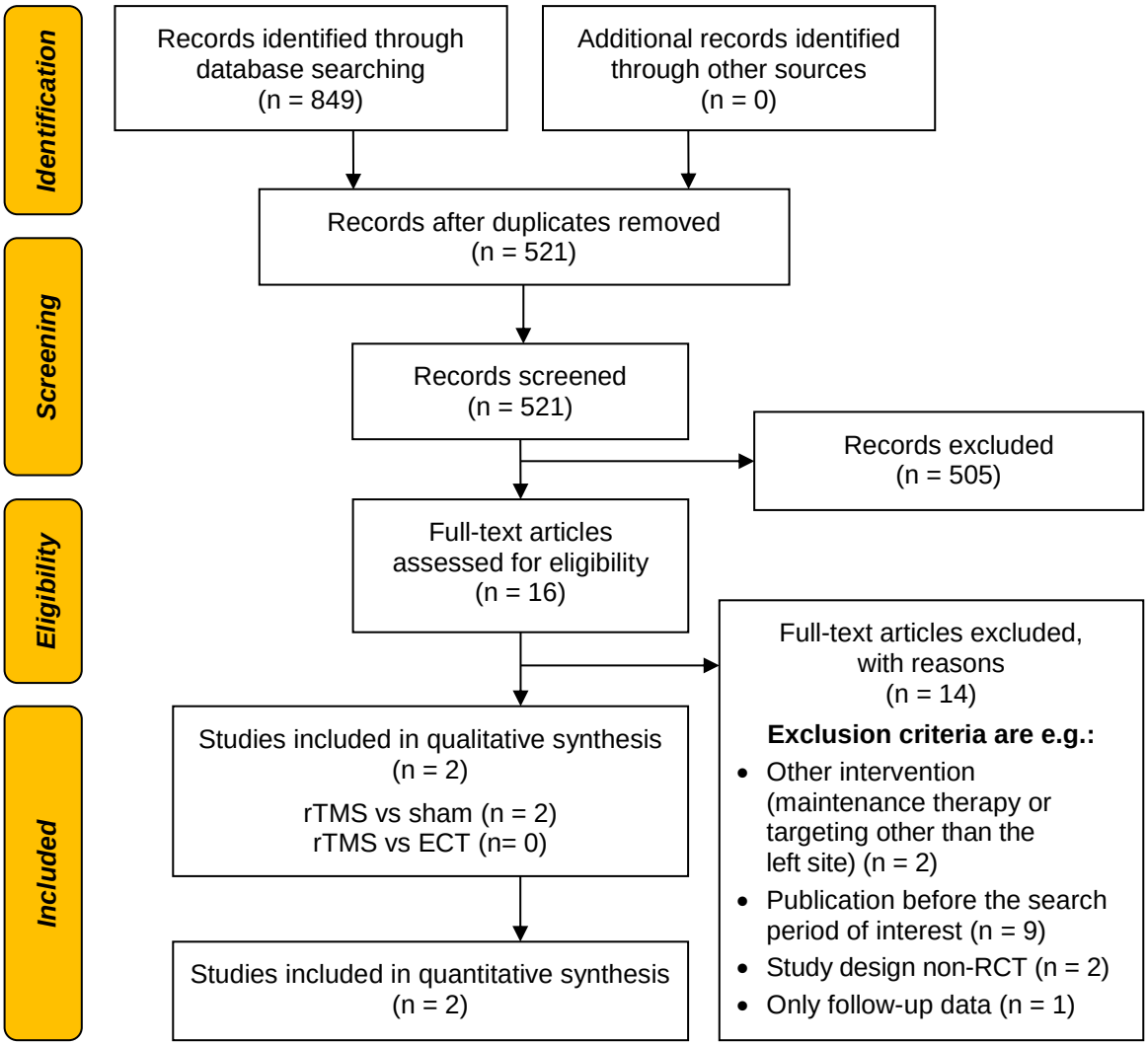

Figure 2: Flow chart for selection of primary studies

The author (LBI-HTA) and the co-author (OSTEBA) screened and selected studies independently from each other. The author checked the discrepancies. Any disagreements were resolved by consensus.

The search yielded 849 records, after deduplication 521 records remained for screening. The reference list was screened by title and abstract to identify potentially relevant studies. A cross-reference search identified no further studies. 2 studies [14, 15] were selected that fulfilled our inclusion criteria and included within the present assessment. The 2 studies compare HF-rTMS to the left DLPFC with sham. No studies were found that compared active stimulation with ECT.

3. Selection of guidelines

We identified guidelines via systematic search and handsearch. The guidelines of the main scientific and professional organizations (American Psychiatric Association/APA, Canadian Network for Mood and Anxiety Treatments/CANMAT, International Federation of Clinical Neurophysiology/IFCN, Royal Australian and New Zealand College of Psychiatrists/RAZCP, and World Federation of Societies of Biological Psychiatry/WSFBP) and the guidelines applicable by professional organizations of the author's (Austria, German Association for Psychiatry and Psychotherapy/DGPPN) and co-author's (Spain, Galician Agency for Health Technology Assessment/AVALIA-t) country of origin were selected to be included in the overview of available guidelines.

2.5 Quality rating of studies

AMSTAR was used to assess the quality of SRs and the Cochrane risk of bias assessment approach was used to assess RCTs (ACROBAT-NRSi tool), according to the EUnetHTA Guidelines on Therapeutic medical devices [26]. For the assessment of the strength of evidence, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [16] approach was used. These steps were performed by the author independently from the co-author(s). Any disagreements were resolved by consensus. The preliminary classification of the importance of the outcomes (GRADE specifies three categories of outcomes according to their importance for decision-making: crucial, important and of limited importance) was done in consensus by the authors.

For Description and Technical Characteristics of Technology (TEC) and Health Problem and Current Use of the Technology (CUR) domains, no quality assessment tool was used, but multiple sources were used in order to validate individual, possibly biased, sources. Descriptive analysis of different information sources was performed. The EUnetHTA submission file from the manufacturers was used as a starting point. The AGREE II tool was used for the quality rating of guidelines. Two authors scored the guidelines independently from each other, disagreements were solved by consensus.

2.6 Statistical-analysis

We conducted a meta-analysis of the pooled results in the R environment [29] using the package ''meta'' [30]. The HQO report [13] used a random effects model for the meta-analysis; we also chose this model in our calculations. The degree of statistical heterogeneity among studies was assessed using the I-squared (I^2) and tau-squared statistics. We calculated changes in depression scores measured by Hamilton Rating Scale for Depression from baseline to the end of treatment and conducted a meta-analysis on the mean changes in scores for the rTMS treatment and control groups. We calculated the effect size as the difference between the means of the two groups divided by the standard deviation (SD), a statistical method known as standardized mean difference (SMD) using Cohen's method. We used Cohen's conventional definition of small, medium, and large effect size as 0.2, 0.5, and 0.8, respectively. Pooled effect sizes for depression scores were calculated in the HQO report using weighted mean difference, the mean difference value of 3.5 points on the Hamilton Rating Scale for Depression was considered to be a clinically relevant treatment effect.

For binary outcomes, we calculated remission and response rates, as well as the pooled risk ratios and risk differences as the summary effect estimates along with their corresponding 95% confidence intervals (CIs) around the point estimates.

2.7 Description of the evidence

Table 2: Main characteristics of the included systematic review for update

Author, year	Study type	Number of patients, number of RCTs	Aim of the study	Intervention(s) vs Comparison(s)	Main endpoints	Inclusion criteria, exclusion criteria	Included studies	Period searched	AMSTAR Score (# no, can't answer, not applicable)
HQO, 2016 [13]	SR	rTMS vs sham rTMS: 1156 pts, 23 RCTs rTMS vs ECT: 266 pts, 6 RCTs	To examine the antidepressant efficacy of rTMS in patients with TRD.	HF rTMS vs sham rTMS, HF rTMS vs ECT	Standardized and weighted mean difference in depression scores, response, remission	Inclusion: RCTs, age ≥ 18 yrs, HF rTMS for ≥ 10 sessions, only unipolar pts or max. 20% bipolar pts, ≥ 80% of pts with TRD Exclusion: Nonrandomised trials stimulation site other than left DLPFC, frequencies outside the range for this review, bilateral or bilateral vs unilateral rTMS, sequential combined LF and HF rTMS, newer technologies (synchronized rTMS, pulsed rTMS, DTMS, rTMS with priming stimulation), studies with only cognitive functions outcome, population: depression due to specific conditions e.g. post stroke, postpartum.	Avery 1999, Avery 2006, Bakim 2012, Berman 2000, Blumberger 2012, Bretlau 2008, Boutros 2002, Chen 2013, Fitzgerald 2003, Fitzgerald 2012, Garcia-Toro 2001, George 2010, Holtzheimer 2004, Hoppner 2003, Loo 1999, Loo 2007, Mogg 2008, Mosimann 2004, O'Reardon 2007, Padberg 2002, Stern 2007, Su 2005, Triggs 2010	1994-2014	9 (#4,5 no)

Abbreviations: AMSTAR A Measurement Tool to Assess Systematic Reviews, DLPFC dorsolateral prefrontal cortex, DTMS deep transcranial magnetic stimulation, ECT electroconvulsive therapy, HF high-frequency, HQO Health Quality Ontario, pts patients, RCT randomized controlled trial, rTMS repetitive transcranial magnetic stimulation, SR systematic review, TRD treatment-resistant depression, yrs years

List of AMSTAR items: (1) Was an 'a priori' design provided? (2) Was there duplicate study selection and data extraction? (3) Was a comprehensive literature search performed? (4) Was the status of publication (i.e. grey literature) used as an inclusion criterion? (5) Was a list of studies (included and excluded) provided? (6) Were the characteristics of the included studies provided? (7) Was the scientific quality of the included studies assessed and documented? (8) Was the scientific quality of the included studies used appropriately in formulating conclusions? (9) Were the methods used to combine the findings of studies appropriate? (10) Was the likelihood of publication bias assessed? (11) Was the conflict of interest included?

The Health Quality Ontario report [13] focused on the assessment of effectiveness and safety of rTMS in patients with TRD. The review covered the time frame from January 1994 to November 2014. 23 RCTs compared rTMS with sham, and 6 RCTs compared rTMS with ECT. The inclusion criteria and exclusion criteria are presented in Table 2**.**

Two new comparative studies were identified by updating the HQO report [13], which are both included only in the effectiveness domain as they contained no safety data. For answering effectiveness domain questions, we considered all studies included in the HQO report and the two new studies identified in the search update, whereas for answering safety questions, we considered only studies from the HQO report that contained safety data. We extracted the studies included in the HQO report as well, because we considered additional outcomes as compared to the HQO report. If stimulation site other than left DLPFC and frequency other than HF was a comparator besides sham and/or ECT, we disregarded the data on that and extracted information only in relation to HF-rTMS and sham and/or ECT.

Table 3: Main characteristics of primary studies included in the update: rTMS vs sham

Author and year or study name	Study type	Number of patients	Intervention(s)	Main endpoints	Included in clinical effectiveness and/or safety domain
Solvason 2014 [15]	RCT	301	HF-rTMS vs sham	Quality of life (Q-LES-Q, SF-36)	Clinical effectiveness
Kang 2016 [14]	RCT	24	HF-rTMS vs sham	HAMD/HDRS score	Clinical effectiveness

Abbreviations: HAMD/HDRS Hamilton Depression Rating Scale**,** HF high frequency, RCT randomized controlled trial, rTMS repetitive transcranial magnetic stimulation, SF-36 Study-36 Item Short Form, Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire

2.8 Deviations from project plan

We deviated from the project plan in the followings: we indicated the device from Brainsway to be considered in the course of the assessment, but we excluded Brainsway because it is a deep TMS device, which is a slightly different type and belongs to the newer rTMS versions. The SR that we selected for update also excluded deep TMS among others. As the selected SR did not define QoL as an efficacy outcome and the included primary studies did not report on it, we also screened primary studies of the last 5 years (2012-2016). We tried to find those studies that might have been excluded from the selected SR in case they did not report on the primary outcomes defined in the SR. Furthermore, we described in the scope that we would include studies in which patients failed at least two trials of antidepressants, but in the primary studies included in the HQO [13] report, nine of them had a less strict inclusion criteria and defined the study population to have failed at least one antidepressant medication.

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What are rTMS, sham stimulation and ECT?
A0020	For which indications rTMS received marketing authorisation or CE marking?
B0002	What is the claimed benefit of rTMS in relation to sham stimulation and ECT?
B0003	What is the phase of development and implementation of rTMS and ECT?
B0004	Who administers rTMS and ECT and in what context and level of care is it provided?
B0008	What kind of special premises are needed to use rTMS and ECT?
B0009	What equipment and supplies are needed to use rTMS and ECT?
A0021	What is the reimbursement status of rTMS?

3.2 Results

Features of the technology and comparators

[B0001] – What are rTMS, sham stimulation and ECT?

Transcranial magnetic stimulation (TMS) is a non-invasive neurostimulation and neuromodulation technique, based on the principle of electromagnetic induction of an electric field (~100V/m) in the brain. The field can be of sufficient magnitude and density to depolarize neurons, and when TMS pulses are applied repetitively they can modulate cortical excitability, decreasing or increasing it, depending on the parameters of stimulation [2, 5].

The equipment consists of a high current pulse generator which produces a discharge current that flows through a stimulating coil, generating a brief magnetic pulse (<1ms) with field strengths up to several Teslas (~4 Tesla) [1, 5].

TMS can be delivered either as a single pulse or as a series of pulses i.e. a train, in which case is called repetitive TMS (rTMS). The depth of the stimulation is approximately 2-3 cm beneath the coil.

The most typical technical parameters of rTMS are the following:

- Frequency: number of magnetic pulses per second (Hz)
  - High (fast) frequency: stimulation delivered >1 pulse per second, but generally ≥ 5 Hz is applied as HF [1, 2]
  - Low (slow) frequency: stimulation delivered at ≤ 1 pulse per second.
- Intensity: expressed as percentage of the resting motor threshold, which is established by stimulating the motor cortex and determining the minimum amount of energy that is required to evoke a motor response in a specific muscle group. The motor response is assessed visually or with electromyography (EEG). Intensity is generally set at 100 to 120 percent of resting motor threshold.
- Train duration (usually 2 s to 4 s)

- Intertrain interval: time between successive trains (usually 8 s to 26 s)
- Number of trains per session
- Number of pulses per session: calculated from the frequency, train duration and number of trains per session [2, 3].

There are various treatment protocols, but the FDA-based standard parameters are most widely used and for the acute treatment they include: 10 magnetic pulses per second (Hz), 3000 pulses per session, 100 to 120 percent of motor threshold, train duration of 4 s with intertrain interval of 26 s [4]. However, the stimulation parameters required to optimize the efficacy of rTMS treatment are not well known. Thus the administration of the treatment is not standardized and the number of necessary treatments is also unclear [3].

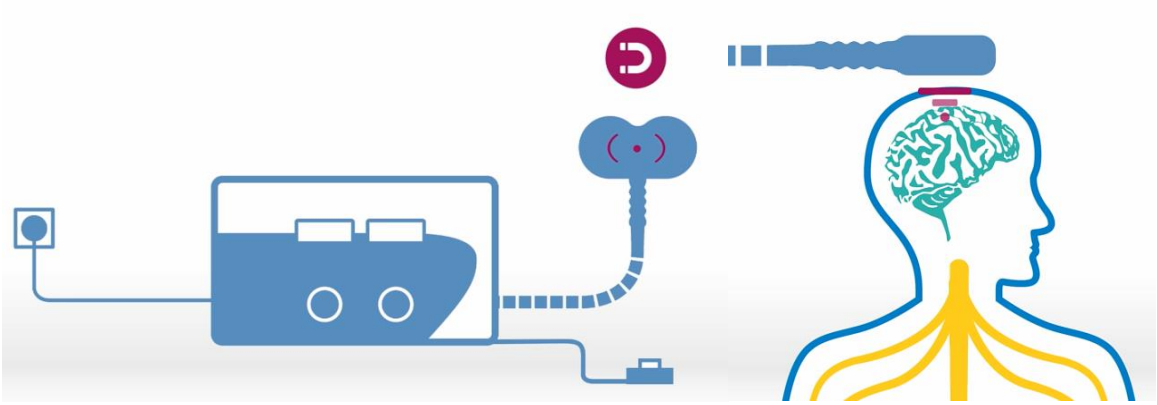

Figure 3: Mechanism of action of rTMS (Source: submission file)

The type and orientation of the coil influences the effect of action. There are several types of coils in use. The large circular coils have a wide action radius. The figure-of-eight coil is for focal stimulation, when the stimulation zone should be only a few square centimetres. The double cone angulated coil, consisting of two large circular coils forming an obtuse angle, can reach deeper targets. There are newer types of coils that allow a lesser rate of decrease of field of magnitude as a function of distance such as the Hesed-coil (H-coil) and the C-core coil, or circular-crown coil among others [31].

The use of the rTMS is prohibited for patients or test subjects with:

- metal implants in the head area, e.g. shunts, clips (for patients with metallic implants or similar objects in the vicinity of the point of treatment, the user must weigh the potential risk against the utility of the treatment),
- implanted medical devices (cochlear implant, medication pump, pacemaker, intra-cardiac lines, etc.),
- during pregnancy (in this case the magnetic nerve root stimulation is of critical importance; the transcranial stimulation is less critical on the basis of the greater distance to the foetus),
- increased intracranial pressure (e.g. after trauma or infection),
- a history of epileptic seizures (only applies for the cortical use; if necessary, a risk/benefit analysis should be performed),
- increased cerebral susceptibility to epileptic seizures through medication (e.g. wellbutrin, zoloft, adderall, fluoxetine, aripiprazole, lithium carbonate, clonazepam),
- unstable general medical disorders [2, 3, 5].

A 13-item clinician-administered questionnaire (Screening 13-item Questionnaire for rTMS Candidates by the International Federation of Clinical Neurophysiology) can be used to screen patients for the contraindications. Psychotic features (delusions and hallucinations) are not a contraindication for treating MDD with rTMS, but most RCTs have excluded psychotic patients [3].

Table 4: Features of the intervention

Proprietary name	Manufacturer	Technical features	Device class/ UMDNS code
Stimulators: Neuro-MS/D Advanced Therapeutic Neuro-MS/D Therapeutic Neuro-MS Monophasic Neuro-MS Paired Monophasic **Coils:** FEC-02-100-C – Cooled figure-of-eight coil FEC-02-100 – Figure-of-eight coil AFEC-02-100-C – Angulated figure-of-eight cooled coil AFEC-02-100 – Angulated figure-of-eight coil RC-02-150-C – Cooled big ring coil RC-02-150 – Big ring coil RC-02-100 – Small ring coil	Neurosoft	**Neuros-MS Monophasic and paired monophasic** are designed to be used for clinical practice and research. The device has a very low electromagnetic interference even during charge and discharge. Thus, it can be used during EEG or ERP recordings. The magnetic stimulator can operate with EMG recorders of most manufacturers (through trig in/out sockets). **Neuro-MS/D Advanced therapeutic** provides the possibility to increase the maximal effective stimulation frequency (each stimulus in series has 100% MT) up to 20 Hz owing to extra power supply unit. Up to 10,000 pulses are generated during one session. A cooling unit and cooled coils are included in the delivery set to avoid overheating of coils during the long treatment session. The cooling unit itself is a tank with the cooling liquid, the pump running the cooling liquid through the coil and the fridge. The unit allows increasing continuous operation up to 10,000 pulses without overheating. Practically, it means that stimulator can operate for hours without overheating. The delivery set includes the special Neuro-MS.NET software that allows customizing any stimulation templates. This software keeps patient database, detects motor response threshold and controls the stimulation courses and sessions.	Class IIa/ UMDNS 12-415
Magstim Rapid^2 70mm Double Air Film Coil Magstim AFC Support Stand Magstim Trolley 70mm Double Air Film Sham Coil	Magstim	**Rapid²** is a compact magnetic stimulator unit, capable of repetitive rate output at high power levels. The system is highly versatile and is compatible with the full range of Magstim coils. The system can be interfaced with different EMG systems. Rapid² also features a unique temperature prediction algorithm that gives users a high degree of confidence that a protocol can be achieved. The **D70mm Alpha coil** utilizes a double figure of eight shape winding to achieve a precise focal magnetic field allowing relatively accurate stimulation of cortical and peripheral structures as compared to circular coils. The profile of the coil allows easy access to most common areas of cortical stimulation and offers superior manoeuvrability. The **Magstim AFC Support Stand** is designed to aid the positioning of a stimulating coil in any desired orientation and can manoeuvre the coil around the subject. The **Magstim trolley** ensures the transport of the stimulators. The **70mm Double Air Film sham coil** allows users to conduct research trials with a true sham condition. By stimulating the peripheral nerves of the face and scalp, the Air Film sham coil looks, sounds, and feels the same as an active coil, both to the subject and operator, but does not deliver active stimulation of deep nerves.	Class II

Proprietary name	Manufacturer	Technical features	Device class/ UMDNS code
PowerMAG 100 clinical PowerMAG 30 clinical rTMS trolley Coil positioning arm Round coil PMR 110 Double coil PMD 70 Double coil PMD70-pCool-SHAM Treatment chair	Mag&More	**PowerMAG 100 clinical** is able to generate burst of pulses up to 100 Hz with constant intensities by recharging between pulses. It also has a maximum pulse frequency of 100 Hz at 70% intensity. The maximal frequency at 100% intensity is 30 Hz. Depending on the type of coil the magnetic induction can reach up to 4 tesla. **PowerMAG 30 clinical** features highly precise, single pulses. It can produce maximum intensity (100% output) in the whole frequency range (0 to 30Hz). **Double coil PMD 70** is suitable for the selective stimulation of individual areas as well as cortical and spinal applications. **Double coil PMD70-pCool-SHAM** has a minimized magnetic field strength, thus enabling the coil to not stimulate the brain, and only stimulate the nearest area (such as scalp) that produces the twitching sensation. Moreover, the coil generates identical sounds compared to the active TMS coils and has a similar weight. **Round coil PMR 110** has the largest stimulation spot within all coils. It also has a high penetration depth. The coil is designed for cortical, spinal, and peripheral applications.	Class IIa
MagPro R30 MagPro R20 MagVita TMS Therapy® System Circular coils Butterfly coils Special coils	MagVenture	**MagPro R30**: 30 pps maximum rep. rate, 60 pps option available **MagPro R20**: stimulation rates up to 20 pps **MagVita TMS Therapy System**: 30 pps maximum rep. rate, chair, and vacuum pillow **Circular coils**: fairly large area of body tissue can be stimulated, usually serves well as a “general purpose coil”. C-100, MC-125, MMC-90, MMC-140, MMC-140-II, MCF-75, MCF-125, Cool-125. The various types differ in the diameter size and the pulses before warmup. **Butterfly coils**: more focused in comparison with the circular coils. The two windings are placed side-by-side, enabling the coil to stimulate structures with focus right under its centre. The butterfly coil is useful in focused stimulation.MC-B35, C-B60, D-B80, MC B65-HO, MC-B70, MCF-B65, MCF-B70, Cool-B35, Cool-B65, Cool D-B80, Cool-B70. The various types differ in the diameter size and the pulses before warmup. **Special coils**: custom designed coils as well as modifications to existing coils, ranging from extending the coil cable, placebo coils, to a complete change of geometry of the coil.	Class II
Neurostar® MS System	Neurostar/ Neuronetics	%MT Range: 80% to 140%MT Pulses per second Range: 0.1 - 30 pps Stimulation Time Range (i.e. pulse train duration): 1-600 seconds for 1 pps, 1-20 seconds for >1 pps Inter-train Interval Range: 0-60 seconds for 1 pps, 10-60 seconds for > 1 pps Pulses per treatment session: Maximum: 5,000, Nominal: 3,000 Coil type: ferromagnetic core	Class II

Abbreviations: MT motor threshold, pps pulses per second, UMDNS Universal Medical Device Nomenclature System
Sources: product descriptions published on the websites of the manufacturers [32-37].

Class II and IIa medical devices are active therapeutic devices intended to administer or exchange energy. Devices classified by this rule are mostly electrical equipment used in surgery (such as lasers and surgical generators), devices for specialised treatment (such as radiation treatment), and stimulation devices, although not all of them can be considered delivering dangerous levels of energy considering the tissue involved [38].

Comparators

Sham stimulation is defined as comparator in the scope of this assessment. Sham stimulation is delivered either with regular TMS coil that is tilted so that an edge remains in contact with the head or with a purpose-built sham TMS coils that resemble regular TMS coils but is equipped with a magnetic shield that attenuates the magnetic field. If a tilted regular coil is used, a sham TMS pulse produces a clicking sound that is very similar to an active TMS pulse and, depending on the geometry and orientation of the TMS coil, the magnetic field can still be sufficiently strong to result in somato-sensory effects. This variant was used in many clinical studies, but the current gold standard seems to be the purpose-built coil combined with surface electrodes for skin stimulation [39].

The critical question is still whether blinding success can be achieved with the combined coil. Several very similar sham TMS setups were developed and their blinding success was evaluated. The general finding of these studies was that electrical stimulation of the skin resulted in somatosensory effects that were very similar to active TMS if the stimulation intensity was individually calibrated. However, the skin sensation was more electric so that experienced participants might have been able to distinguish between active and sham TMS. Indeed, naïve participants have been found to mistake sham TMS for active TMS, whereas experienced participants can tell them apart. These results indicate that sham TMS approaches might suffice for clinical applications where patients are generally naïve to differences between active and sham TMS, in which case a blind research design is achieved (operator, the patient and the investigators are blinded). Nevertheless, the sham approaches require further developments and efficient blinding should be controlled for by systematically questioning the patients about their guess as to group allocation [1, 39].

Electroconvulsive therapy involves the induction of a convulsion (seizure) by the application of electrical current to the brain. It is delivered under general anaesthesia and application of a muscle relaxant. The exact mechanism of action is still unclear and it is under investigation, but the most likely hypothesis includes seizure-induced changes in neurotransmitters, neuroplasticity, and parameters include electrode position, electrical intensity, pulse width, and duration. The most common electrode placements are bilateral, or right unilateral. The electrical intensity is based on the minimum intensity to produce a generalized seizure, called the seizure threshold. ECT usually uses brief pulse width (0.25 to 2 ms) and duration (0.5 to 8 or more seconds) [6]. ECT is a complex intervention and its efficacy and safety are affected by a number of parameters including the placement of electrodes, dosage and waveform of the electrical stimulus, and the frequency with which ECT is administered [7].

As regards to mortality, ECT is a safe procedure with a very low mortality rate (1 death per 73.440 treatments), approximating the risk of general anaesthesia. The absolute contraindication for ECT is intracranial hypertension, however, patients with myocardial ischemia, cardiac arrhythmias, space-occupying cerebral lesion, increased intracranial pressure, recent cerebral haemorrhage, unstable vascular aneurysm or malformation, abdominal aortic aneurysms, pheochromocytoma, and class 4 or 5 anaesthesia risk are also more likely to be harmed as they carry a higher morbidity and mortality risk [6].

ECT is frequently associated with cognitive impairment including transient disorientation when recovering from ECT sessions, retrograde amnesia, anterograde amnesia, mild-, short-term impairment in memory and other cognitive domains during and after treatment with ECT. However, these impairments are normally transient and the cognitive functioning recovers within weeks or months after the acute course of ECT [6, 8].

[A0020] – For which indications has rTMS received marketing authorisation or CE marking?

TMS is indicated for patients with unipolar major depression who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode. Detailed information on the regulatory status of the included products is included in Table A13 in Appendix 2.

[B0002] – What is the claimed benefit of rTMS in relation to sham stimulation and ECT?

rTMS is a non-invasive procedure in which the patient remains awake and alert throughout. There is no post-session recovery needed, the patient can resume normal activities immediately. No cognitive side-effects have been reported with rTMS, unlike with ECT. [6, 8].

[B0003] – What is the phase of development and implementation of rTMS, sham stimulation and ECT?

TMS was developed by Barker in 1985 in Sheffield, England. He created a focal electromagnetic device with sufficient power to induce currents in the spine. He also realized that the device was appropriate for the direct and non-invasive stimulation of the brain. The device was first used in research and then became a therapeutic device [8]. The first device to gain FDA approval was NeuroStar TMS Therapy System in 2008 [40].

The use of functional imaging is a new development to help in better predicting the response to rTMS treatment through evaluating the cortical excitability. Combining TMS with brain imaging techniques such as PET and resting fMRI or neuropsychological techniques like EEG could be used for this purpose. They permit direct quantification of evoked cortical activation generated by single TMS pulses. Therefore, it can be used as a marker of therapeutic response, it may help to optimize the treatment effects, to better understand the pathopsychology of the disorder and the mechanism of action of the technology [1, 2, 41].

Another novelty is an oscillating weak TMS device that is being currently tested, which might enable home delivery of TMS (under a doctor's prescription) because it would likely be unable to cause a seizure [31].

There are several experimental techniques representing variations of rTMS.
These are the followings:

- Accelerated rTMS: instead of the one session with 3,000 pulses per day administration of rTMS, two sessions with 1,500 pulses each are administered daily.
- High-dose rTMS: more pulses than usual over the same treatment time frame (e.g. 6,000 pulses per session).
- Theta burst rTMS: 50 Hz burst of rTMS delivered five times per second.
- Deep rTMS: brain structures are stimulated beneath the superficial prefrontal cortex using a magnetic coil (H-coil) that can induce a magnetic field with a deeper and wider distribution than standard figure 8 coils.
- Bilateral rTMS: HF of the left DLPFC stimulation is combined with LF of the right DLPFC stimulation (either simultaneously or sequentially).

- Syncronized rTMS: the stimulation is synchronized to an individual's alpha frequency, which allows the use of lower magnetic field energy leading to greater patient comfort during stimulation.
- Priming rTMS: delivering HF-TMS before LF-TMS to try to boost LF-TMS effectiveness. [3].

Comparators

Sham stimulation coils have been marketed since the 2000's based on different technical solutions. The sham coils used to produce almost no scalp sensations, therefore, even less perceptive patients might have found out if they received active or sham treatment. The first development of sham coils included a system that produced a cutaneous electrical stimulation.

ECT has been in practice since the 1930s. The practice of ECT has undergone a number of modifications since its introduction and it has established standards. With the present-day technique, many of the previously significant medical complications of ECT have been eliminated [13].

[B0004] – Who administers rTMS, sham stimulation and ECT and in what context and level of care are they provided?

A physician should perform the initial motor threshold determination and identify the appropriate coil location for subsequent treatments. The individual daily treatment sessions, including subsequent motor threshold determinations, can be administered by a nurse, physician assistant, or medical assistant. That applies as long as the physician is accessible via telephone in case of emergency and as long as he supervises the treatment through evaluating the clinical course of the daily treatment sessions to determine if any modifications are necessary and to respond to any possible adverse events. Manufacturers' training should be provided to all operators both on the technology itself and on the specific TMS system to be used. In addition, all personnel should have cardiopulmonary or basic life support training to be able to recognize and initially manage generalized seizures. The operator should provide updates, progress notes, or both every day to the prescribing physician for monitoring purposes. Mood scales are recommended to be used to document the changes in depression [2, 3, 42].

rTMS is usually administered 5 days a week on an outpatient basis in a hospital or appropriately equipped outpatient clinic. The course of treatment lasts from 10 to 30 sessions, administration is labour-intensive and time-consuming for both the patients and clinicians [2, 8]. Am session lasts typically 30-40 minutes [3]. There is however no validated standard protocol on how many sessions are needed to reach maximal effect. Clinical experience suggests 20 sessions before declaring treatment failure [6].

ECT requires a number of different specialists to be involved. The staff should comprise of an an-aesthesiology nurse, a psychiatric nurse, plus 4 untrained nurses or nursing assistants, an anaesthesiologist, a psychiatrist and an operating department assistant [43]. According to clinical experts, ECT treatment takes about 25-40 minutes (5-10 minute treatment and 20-30 minutes preparation and post-treatment routine). ECT may only be performed by a psychiatrist who is experienced with this treatment intervention [21]. ECT is typically conducted on inpatients, but outpatient (ambulatory) ECT practice is growing, largely because of its increasing use for continuation and maintenance treatment [24]. ECT is typically delivered 2-3 times per week and the number of treatments sessions to achieve response/remission ranges between 6 and 15.

More than 3 treatments per week are not recommended as they are associated with higher frequency of cognitive side effects [6].

[B0008] – What kind of special premises are needed to use rTMS, sham stimulation and ECT? and

[B0009] – What equipment and supplies are needed to use rTMS, sham stimulation and ECT?

For the use of rTMS, a silent room equipped with a reclining chair is needed. The equipment consists of a generator and a coil. Sometimes, neuronavigation guided by MRI is used to localize the prefrontal cortex. During the treatment session, the magnetic pulse produces a clicking sound, which varies with different coil designs and intensity. For hearing protection, the use of ear plugs or other hearing protection capable of at least 30 dB sound reduction is recommended both for the patient and the treatment provider. The room where the treatment is administered should be equipped with oxygen and anticonvulsant medications in case a seizure occurs. Besides the stimulator and the coil, no further accessories are required. Optional accessories are e.g. a cap to indicate the patient's therapy hot spot, an EMG device, a positioning arm for the coil, or a vacuum cushion to stabilise the patients' head [2, 3, 5].

ECT is delivered in a controlled clinical setting under general anaesthesia and after application of a muscle relaxant. The minimum requirement for ECT facilities is three rooms: a quiet, comfortable waiting area, a treatment room and a recovery area of a sufficient size to accommodate the rate and number of patients treated per session (possibly up to six patients lying on trolleys). The rooms should contain the necessary equipment to monitor patients and treat them in an emergency. The machines currently recommended for use by the APA and the Royal College of Psychiatrists are Mecta SR2 and JR2, Thymatron-DGx and Ectron series 5A Ectonus machines [7].

[A0021] – What is the reimbursement status of rTMS?

Detailed information on the reimbursement status/recommendations can be found in Table A14 in Appendix 2.

3.3 Discussion

The technology is still lacking consensus guidance on the stimulation protocols to be used to avoid suboptimal adjustments in order to reach optimal treatment outcomes. There are several technical variables that contribute to variable treatment protocols: the frequency (low or high), the stimulation site (right, left, mixed) and if it is bi-or unilateral, the number and duration of trains, pulses per session, intertrain intervals, and the intensity of the stimulation. We considered studies that applied unilateral high-frequency stimulation to the left DLPFC in both the sham controlled and the ECT comparison studies. In TRD treatment, ECT is used bilaterally because it is more efficacious than unilaterally used ECT. It is yet still unproven if the same applies to the rTMS treatment [7].

The treatment intensity is influenced by the coil to cortex distance. The standard protocol followed by trials, based on the earliest TMS studies, includes the localization of the motor cortical site that results in maximal activation of a peripheral hand muscle and the subsequent measuring of 5 cm

anterior along a parasagittal line over the scalp surface (called the 5 cm method). Recent studies have re-evaluated this method and found that it may be suboptimal (anatomically incorrect) and therefore limiting the treatment potential of rTMS. If the coil is not placed at the right area (i.e. the prefrontal cortex rather than the premotor cortex or the frontal eye field), the stimulation intensities need to be adjusted as they might be too high, contributing to subject discomfort, increased incidence of headaches, facial pain, and might result in higher incidence of drop-out. Additionally, overstimulation of the cortex lessens the focality delivered by the figure-of-8 coil, which may confound treatment results. On the contrary, if stimulation is delivered at a too low intensity, the efficacy of the treatment might be compromised. The optimization of the intensity can be best achieved through the adjustment of the coil to cortex distance [1, 41]. For coil navigation, magnetic resonance imaging guidance is the most precise method, however, scalp-based navigation is still the most common [6].

Other variables that might influence treatment effectiveness are treatment duration, the type of coil, and if the treatment is delivered as a mono-or add-on therapy [41]. The newest coil types, including the H-coil that can deliver stimulation that can reach deeper brain areas than the conventional coils, are still under investigation and, although H-coil of Brainsway already received CE mark and FDA approval, they are not yet discussed in CPGs.

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

Element ID	Research question
A0002	What is treatment-resistant major depressive disorder?
A0003	What are the known risk factors for treatment-resistant major depressive disorder?
A0004	What is the natural course of treatment-resistant major depressive disorder?
A0005	What are the symptoms and the burden of treatment-resistant major depressive disorder for the patient?
A0006	What are the consequences of treatment-resistant major depressive disorder for the society?
A0024	How is treatment-resistant major depressive disorder currently diagnosed according to published guidelines and in practice?
A0025	How is treatment-resistant major depressive disorder currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is rTMS utilised?

4.2 Results

Overview of the disease or health condition

[A0002] – What is treatment-resistant major depressive disorder in the scope of this assessment?

Treatment-resistant major depressive disorder (TRD) often refers to major depressive disorder (MDD) that does not respond satisfactorily to at least two trials of antidepressant monotherapy. However, the definition has not been standardized yet. Defining treatment resistant depression is also complicated due to the lack of consensus in describing acute antidepressant responses. In many studies, response is classified according to the amount of improvement from baseline on the depression rating scale.

- No response – improvement < 25 percent
- Partial response – improvement 25 to 49 percent
- Response – improvement ≥ 50 percent, but less than the threshold for remission
- Remission – depression rating scale score less than or equal to a specific cut-off that defines the normal range (score on the HRSD-17 or on the MASD ≤ 7) [9].

[A0003] – What are the known risk factors for treatment-resistant major depressive disorder?

Treatment resistant, unipolar major depression has been associated with many risk factors, including:

- Comorbid general medical disorders like coronary heart disease, hypothyroidism, diabetes, HIV infection etc.
- Chronic pain
- Medications (e.g. interferons and glucocorticoids)
- Comorbid psychiatric disorders
    - Anxiety: affects the speed to response to medication and remission of symptoms. A history of any anxiety disorder predicts a significantly slower rate of recovery. Thus, the clinical evaluation of treatment-resistant depression must include screening for anxiety symptoms and disorders.
    - Substance abuse: acute and chronic effects of substances may cause or worsen depressive symptoms, affect compliance, and contribute to treatment resistance. Furthermore, the presence of a mood disorder increases the likelihood of a substance use disorder or makes the patient more prone to relapse.
    - Personality disorders: evidence indicates that depressed patients with personality disorders are less responsive to antidepressant therapy compared to patients with no Axis II pathology and have a worse prognosis for long-term outcomes [44].
- Severe intensity of depressive symptoms
- Suicidal thoughts and behaviour
- Adverse life events (e.g. marital discord)
- Early age of onset of major depression (e.g. age <18 years)
- Recurrent depressive episodes
- Low socioeconomic status
- Gender (female)
- Family history

Studies have found that the association of other factors with treatment resistance is inconsistent and thus less clinically useful [9, 44].

[A0004] – What is the natural course treatment-resistant major depressive disorder?

Symptoms of MDD develop over days to weeks. In some individuals, prodromal symptoms, including generalized anxiety, panic attacks, phobias, or depressive symptoms that do not meet the diagnostic threshold, may occur over the preceding several months. Yet in others, MDD may develop suddenly, as a result of severe psychosocial stress. The duration of a major depressive episode also varies. In treated patients, the median time to recovery is approximately 20 weeks; in untreated patients, however, it can last 6 months or longer. Major depressive episode is unremitting in 15% of patients and recurrent in 35%. About half of the patients with a first onset episode recover and have no further episodes. After 3 episodes, the risk of recurrence is close to

100% in the absence of prophylactic treatment. The course of recurrent major depressive episodes also varies [21].

Effects of the disease or health condition

[A0005] – What are the symptoms and the burden of treatment-resistant major depressive disorder for the patient?

The most serious complication of a major depressive episode is suicide (including suicide/homicide). MDD is also associated with significant medical comorbidity and it complicates recovery from other medical illnesses, such as myocardial infarction [21].

Comorbid conditions are more prevalent among TRD patients. They include joint, limb, or back pain, hypertension, dyslipidaemia, malaise or fatigue, anxiety, and personality disorder. Suicidal ideation is estimated to a rate of 15% ± 8% in TRD patients, 6% in treatment-responsive depression, and 1% in the general population [45]. Medication-related adverse events like decreased sexual desire, orgasmic dysfuntion, blurred vision, dissociative reactions, ataxia, mixed states (dysphoric mania or agitated depression), tremor, and nausea also burden MDD patients.

[A0006] – What are the consequences of treatment-resistant major depressive disorder for the society?

The WHO ranks MDD among the diseases that are most debilitating to the society, partly because of the increased utilization of health care resources, diminished quality of life, and indirect personal and societal costs associated with it [46].

Beyond the impact of MDD on the patient alone, it also affects the patient's social network, including children, spouse, parents, friends, colleagues, and significant others. If the patient is a parent, the disorder may affect his or her ability to fulfil parental role expectations and increase the likelihood of children becoming depressed as well. Major depressive episodes are associated with occupational dysfunction, including unemployment, absenteeism, and decreased work productivity. In fact, in terms of the level of disability for the population as a whole, MDD is second to chronic back and neck pain in disability days per year in the WHO ranking [21, 46].

The annual added social cost of MDD consists of the frequent visits to medical facilities, higher rate of hospitalization, higher costs of antidepressant medications, psychotherapy, other therapies, and indirect costs of lost productivity for both patients and their family members [12, 45]. According to a study on the economic burden of TRD, due to higher health care utilization TRD is associated with 29.3% higher per-patient medical costs than non-TRD [47].

Current clinical management of the disease or health condition

[A0024] – How is treatment-resistant major depressive disorder currently diagnosed according to published guidelines and in practice?

MDD is currently diagnosed by using the Diagnostic Criteria for Major Depressive Disorder and Depressive Episodes (DSM-IV-TR) (details in Appendix 4).

Because of differences in treatment, the diagnosis of unipolar major depression should be confirmed and other diagnosis such as bipolar depression or dysthymic disorder ruled out. The treatment history of patients who may be treatment resistant is usually assessed through a clinical

interview as well as a review of the medical record, i.e. the antidepressant treatment history form [9, 48, 49].

As underpinned by several studies, approximately 50% of MDD patients do not respond to the first course of antidepressant treatment and remission rate is about 37% [8, 9]. There is some variability in the number and type of treatment failures that constitute to the presence of TRD. Many guidelines refer to TRD as patients who have failed to respond to at least two adequate trials of antidepressant medications from different drug classes. In addition, various TRD staging models have been designed as a means of measuring TRD severity [11]. Thase and Rush developed a staging system that is an aid in the application of treatment strategies in a stepwise fashion. The Maudsley Staging Method is also used in staging treatment resistance. It is a points-based staging model incorporating 3 factors: treatment, severity of illness, and duration of presenting episode. The overall level of resistance estimated using this model varies from minimal to severe resistance. The rating system allows specifying categories: mild (score of 3), moderate, and severe (score of 15), based on severity of resistance [50].

TRD Stage	Criteria
Stage 1	Failure of an adequate trial of 1 class of major antidepressant
Stage 2	Failure of adequate trials of 2 distinctly different classes of antidepressants
Stage 3	Stage 2 plus failure of a third class of antidepressant, including a tricyclic antidepressant
Stage 4	Stage 3 plus failure of an adequate trial of a monoamine oxidase inhibitor
Stage 5	Stage 4 plus failure of an adequate course of electroconvulsive therapy

Figure 3: Thase-Rush Treatment-Resistant Depression (TRD) Staging Method. Source: [12]

In the diagnostic process, the first step is to rule out pseudoresistance. Factors to be considered in this process can be divided into three areas: physician factors, patient factors, and accuracy of the diagnosis. The physician factors mean the prescribing habits of doctors (not increasing the dosage levels or discontinuing the antidepressant before an adequate trial has been completed are two major causes that contribute to pseudoresistance). Patient factors include premature discontinuation of medication, unusual pharmacokinetics, patient noncompliance, which often remains hidden. It has been estimated that up to 20% of TRD might be attributable to non-adherence. Frequent examples for the third factor, misdiagnosis, are substance-induced mood disorders secondary to alcohol, substances, or medications, and depression secondary to medical conditions such as hypothyroidism. The presence of unrecognized depressive subtypes should also be carefully evaluated because they need a different treatment approach [12, 44].

From a healthcare provider point of view, clinicians must work through the treatment algorithm in a timely manner and ensure that the patient adheres to the treatment strategy before pronouncing it resistant to a strategy and going on with the subsequent one. The duration of an adequate trial should last 6-12 weeks before deciding if a regimen has sufficiently relieved symptoms. For patients who show little improvement (less than 25% reduction of baseline symptoms) after 4-6 weeks, next step treatment is administered [51].

[A0025] – How is treatment-resistant major depressive disorder currently managed according to published guidelines and in practice?

Many clinical practice guidelines (CPG) address depression management. Nevertheless, despite how common it is that depressed patients experience at least two unsuccessful treatment attempts, at this point in time, no single guideline has treatment-resistant depression as its main (or even secondary) topic. The available guidelines are presented in Table A 1 and Table A2 in Appendix 1.

From the above, it is clear that there is a lack of internationally accepted treatment algorithm both for the treatment of MDD generally and for the management of TRD.

Summarizing the similarities in the guidelines, the treatment strategies for patients with unipolar major depression who do not respond adequately to initial treatment with an antidepressant medication include five main strategies [52]:

1. *optimization:* Maximize dose for adequate time and check serum levels of prescribed antidepressant if supported by evidence based data
2. *switching:* Changing from one ineffective antidepressant to similar or different class of anti-depressant; selective serotonin reuptake inhibitors (SSRI)/serotonin-norepinephrine reuptake inhibitors (SNRI) to tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), and atypical antipsychotics with antidepressant properties
3. *combination:* adding another antidepressant from different classes, eg, TCA + MAOI, SSRI + TCA, SSRI + atypical antidepressant, SSRI + buspirone, etc
4. *augmentation:* adding a second agent that is not an antidepressant, but may enhance the antidepressant effect of the drug in question, eg, lithium, thyroid hormones, pindolol, psycho-stimulants, atypical antipsychotics, sex hormones, anticonvulsants/mood stabilizers, and dopamine agonists
5. *somatic therapies:* ECT, vagus nerve stimulation (VNS), rTMS, magnetic seizure therapy (MST), deep brain stimulation (DBS), and transcranial direct current stimulation (TDCS)

Adapted from the guidelines, the following treatment hierachy was considered for the assessment: **First-line treatment** of MDD is usually an SSRI and psychotherapy. If the patient is resistant to this treatment, the first strategy is *optimization*.

Second-line treatment strategies: for mild to moderate depression that is treatment resistant

1. *Switching* antidepressants: many options are available, the most common ones:

- SNRIs e.g. venlafaxine
- Atypical antidepressants e.g. buproprion, mirtazapine
- TCAs e.g. imipramine, nortriptyline
- MAOIs e.g. tranylcypromine, phenelzine

When choosing the antidepressant, the treatment history, comorbid general medical conditions, patient preference, and costs are also considered.

2. *Augmentation*: for patients who obtain little symptom relief (reduction of baseline symptoms by less than 25%), augmentation is recommended as the second-line treatment. The most common options for augmentation are:

- Second-generation antipsychotics

- Lithium
- Thyroid hormone
- Second antidepressant from a different class

Third-and subsequent-line treatment strategies: for patients who do not respond satisfactorily to several courses of first- and second-line treatments:

- rTMS
- ECT
- Other somatic therapies e.g. VNS, DBS
- Augmentation with omega-3 fatty acids, folate, S-adenosyl methionine, or pramipexole [12, 51, 53].

Target population

[A0007] – What is the target population of this assessment?

Patients with unipolar treatment resistant major depression are the target population of the current assessment. TRD is typically limited to patients who meet criteria only for unipolar MDD [12]. It is important to differentiate between unipolar and bipolar depression because the pathopsychology and the treatment mechanism to be applied differ. Antidepressant interventions are associated with a risk of triggering mania in bipolar depression. Currently, there is no sufficient data to establish recommendations regarding rTMS for bipolar depression [1].

[A0023] – How many people belong to the target population?

The prevalence of unipolar treatment resistant major depression is not clear due to the lack of internationally acknowledged and standardized definition. However, based on the Thase-Rush TRD Staging Model, there are reasonable estimates available for Stage 1 and 2 TRD. The prevalence estimate varies according as response or remission is used as the criterion outcome.

If response is used as outcome, according to the definition of response, the prevalence rate for Stage 1 patients is 30-40% or 50% (unresponsive to or do not benefit from the first trial of antidepressant medication) [1, 8, 12, 44]. Stage 2 TRD (failure to achieve response criteria after 2 courses of adequate treatment) may be estimated to occur in approximately 15-35% of patients [1, 11, 12].

If remission is used as outcome, based on the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the prevalence rate for Stage 1 TRD (patients who fail to obtain a complete remission after one adequate trial of antidepressant) has been reported to be 60 to 70% [9, 12].

In Austria, 120.000 to 140.000 patients per year are diagnosed with depression, from which only 24.000 to 36.000 are treated sufficiently [54]. From the rest 84.000 to 116.000 patients, response will not occur in 8.400 to 17.400 people, taking the 10-15% estimation into account.

[A0011] – How much is rTMS utilized?

We found no data and were not provided information by the manufacturers on the utilization of rTMS.

4.3 Discussion

The inconsistent definition of treatment resistance, diagnostic, and treatment heterogeneity pose difficulties to the comparison among studies. The overlaps of the numerous TRD definitions include that TRD is characterized by the syndrome of unipolar depression, the failure of antidepressant medication, each antidepressant medication trial being adequate in terms of dose, duration, compliance and tolerability, and the absence of physical illness or psychosocial dysfunction, which should be the primary focus of the treatment. The differences include, for example, the number of failed adequate trials of antidepressants (one or two) and the duration of the trial (6 or 6-8 weeks). The staging/severity also varies between 5 and 7 stages, depending on the number and type of physical therapies used [55].

The lack of consensus criteria and definition of TRD also results in the lack-of agreed-upon estimates of prevalence. There are different prevalence rates corresponding to each TRD stage. The estimates of TRD prevalence also vary greatly depending on the treatment setting in which the estimate is made. The tendency is that the rate is the lowest in primary care setting, becoming progressively higher in outpatient psychiatry setting, inpatient psychiatry setting, and academic care setting [12].

An additional problem is that many patients labelled with TRD actually have pseudoresistance due to inadequate treatment or misdiagnosis, unrecognized comorbid psychiatric or general medical conditions [44].

There is no consensus about several issues amongst all the clinically useful outcome criteria (if response, remission, or complete recovery is the best outcome), if each antidepressant treatment should have a different mechanism of action, where the newer treatments like rTMS or vagus nerve stimulation etc. should be included in the staging scheme, and whether stage 4 and 5 TRD might constitute a unique depressive subtype [12]. Patients in stage 2 through stage 5 have the greatest unmet need and trials have focused mainly on patients who are in stage 1 or even prior to stage 1 [8].

The appropriate place of this technology in the therapeutic decision tree is also not yet clearly defined [1]. The main difference in the recommendations of the various guidelines is the place of rTMS in the treatment algorithm: expands from first-line recommendation to third-line. ECT is also recommended either as first-line for those who need rapid response due to high suicidal risk or second-to subsequent-lines in the various guidelines.

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

Element ID	Research question
D0001	What is the expected beneficial effect of rTMS on mortality?
D0005	How does rTMS affect symptoms and findings (severity, frequency) of treatment-resistant major depressive disorder?
D0006	How does rTMS affect progression (or recurrence) of treatment-resistant major depressive disorder?
D0011	What is the effect of rTMS on patients' body functions?
D0016	How does the use of rTMS affect activities of daily living?
D0012	What is the effect of rTMS on generic health-related quality of life?
D0013	What is the effect of rTMS on disease-specific quality of life?
D0017	Were patients satisfied with rTMS?

5.2 Results

Included studies

rTMS vs sham

23 studies met the inclusion criteria in the HQO report [13]. We found additional two RCTs [14, 15] that met our inclusion criteria and are included in the present analysis. One of them [15] is the 6 month follow-up of a study included in the HQO report [17]. A total of 1180 patients were analysed in the studies, 615 in the active rTMS arm and 565 in the sham arm. The HQO report did not include two studies [56, 57] that failed to comply with the safety guidelines in terms of the maximum duration of trains and number of pulses delivered. A few other studies [17, 58-60] also slightly exceeded the maximum duration of trains and the number of pulses delivered, but they applied lower frequencies. Therefore, they were kept in the analysis. A few studies used intensity below 80% MT, which is not addressed in the safety guidelines [2]; they were also kept in the analysis. 17 studies reported depression scores at baseline and at the end of treatment. Baseline depression scores in the rTMS group measured on the HDRS-17 ranged from 19 to 28, and in the sham group it ranged from 21 to 27. In 11 studies, the mean depressive symptoms at baseline were above 25, indicating severe depression. In the remaining studies, the mean depression score ranged from 19 to 24, indicating a moderate depression severity. In 16 studies, patients had failed to benefit from two or more antidepressant medications, nine studies also included patients who had failed to improve after at least one antidepressant medication. In 17 studies, patients received rTMS while receiving antidepressants and in eight studies, patients did not receive any antidepressants during the treatment. 14 studies did not include any bipolar patients, 10 studies included also bipolar, but only to the extent of 1.7 to 16.7% of all participants of the study, and one study did not report on the inclusion of bipolar patients. The frequency of stimulation ranged from 5 to 20 Hz, the intensity was between 80 and 120% of patients' MT. The number of trains per session ranged from 15 to 75, and the train duration was between 2 to 10 seconds. The number of pulses per session ranged from 800 to 3,000 and the total number of pulses during rTMS treatment ranged from 8,000 to 90,000. The inter-train interval varied across studies and ranged from 22 to 58 seconds. All studies used the figure 8 shape coil.

Details of the RCTs can be found in evidence tables Table A5 in Appendix 1.

rTMS vs ECT

Six studies were found by authors of the HQO report [13] that compared rTMS with ECT. Most of the studies were conducted in the early 2000s. The total number of patients was 266, 133 in each arm. Two of the studies reported 6 month follow-up data as well [18, 19]. Four studies reported that the outcome assessors were blinded, in two studies they were not blinded, of which one study [61] did not comply with the safety standards and therefore was not included in the meta-analysis. The mean age of patients ranged from 34 to 68 years, predominantly women. In two studies patients were taking medication during the trial, in two studies patients were completely medication-free and in two trials patients were allowed to take lorazepam or clonazepam during the trial. Two studies reported that patients failed to benefit from two antidepressant trials, while two studies did not state the number, but include how many patients failed ECT before the trial, one study reported that patients failed at least one antidepressant trial and one study reported the number of failed antidepressants in the current episode. Baseline depression scores measured on the HDRS-17 ranged from 24 to 26 in the rTMS group and 25 to 28 in the ECT group. Only one study reported on suicide scores. The characteristics of the intervention varied also, one study used 20 Hz frequency stimulation, four studies used 10 Hz and one study did not report on the frequency used. The intensity of the stimulation ranged from 90 to 110% of the MT, the number of trains from 20 to 30-35, the train duration from 2 to 10 s, the intertrain interval from 20 to 55 s, the pulses per session from 408 to 2,500 and the number of sessions from 10 to 20. Hence the total number of pulses delivered also ranged from 4,080 to 50,000. All studies reported that they used a figure 8 coil.

Details of the single RCTs can be found in evidence tables Table A 6 in Appendix 1.

Mortality

[D0001] – What is the expected beneficial effect of rTMS on mortality?

Three studies in the HQO report [13] included data on suicide scores or suicidal ideations. We identified no new studies reporting on suicide. One of these studies [20] compared rTMS with ECT. The suicide score decreased from 1.5 (0.8) to 1.2 (0.9) as measured by BDI and from 1.9 (1.3) to 1.4 (1.2) as measured by HDRS in the rTMS group. In the ECT group the decrease was significantly greater: from baseline 1.4 (1.0) to 0.5 (0.7) as measured by BDI and 2.3 (1.1) to 0.3 (0.5) as measured by HDRS ($p<.001$). The results suggest that ECT decreases suicidal scores more than rTMS. The other two studies compared rTMS with sham rTMS [17, 62] and reported that no death occurred, but a single suspected suicide gesture in the sham group [17], respectively in the active stimulation group [62] was observed.

Morbidity

[D0005] – How does rTMS affect symptoms and findings (severity, frequency) of treatment-resistant major depressive disorder?

rTMS vs sham

The mean difference in depression scores was reported in 15 studies that complied with the safety standards. Hence, only data from these studies were included in the meta-analysis. We found one additional study [14] that met our inclusion criteria. Since the authors of the new study

didn't report the standard deviation, a new meta-analysis for this outcome was not justified. The authors of the HQO report [13] calculated the weighted mean difference of depression scores from baseline to the end of treatment, which is 2.31 points (95% CI 1.19-3.43), p<.001) favouring rTMS. There was a low degree of heterogeneity among studies (I^2=19.8%, p=.223). On average, rTMS reduced depression scores by about 2.31 points more than sham, which is below the mean value that was deemed a priori clinically important (threshold of 3.5 points). The standardized mean difference was calculated using Cohen's method and the effect size was 0.33 (95% CI 0.17-0.5, p<.001) with a low degree of heterogeneity among studies (I^2=14.7%, p=.289).

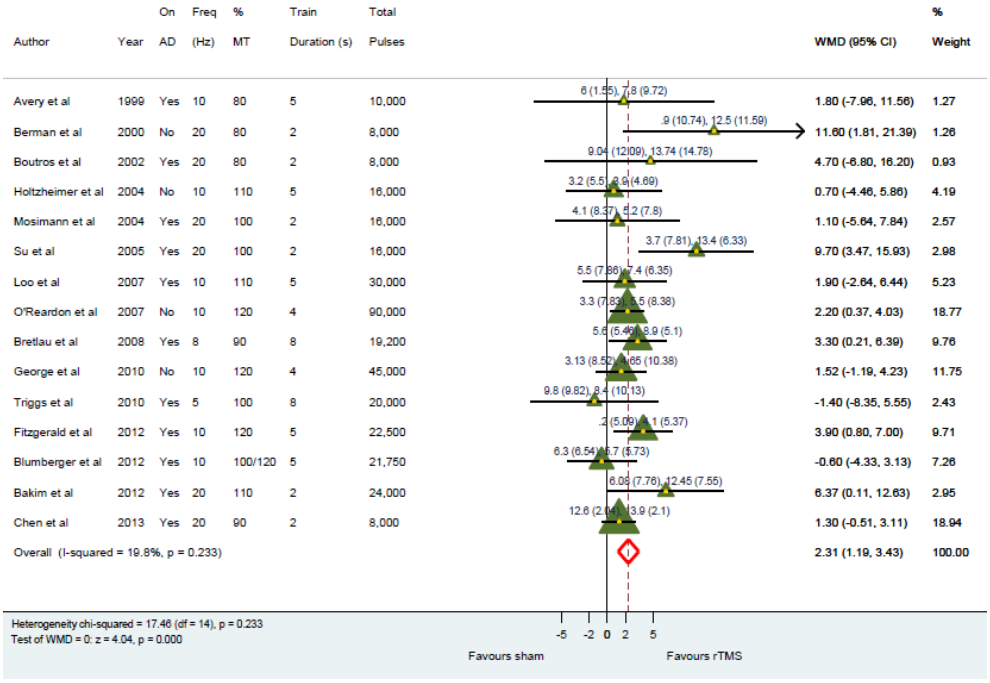

Figure 4: Weighted mean difference: rTMS vs sham (Source: HQO [13])

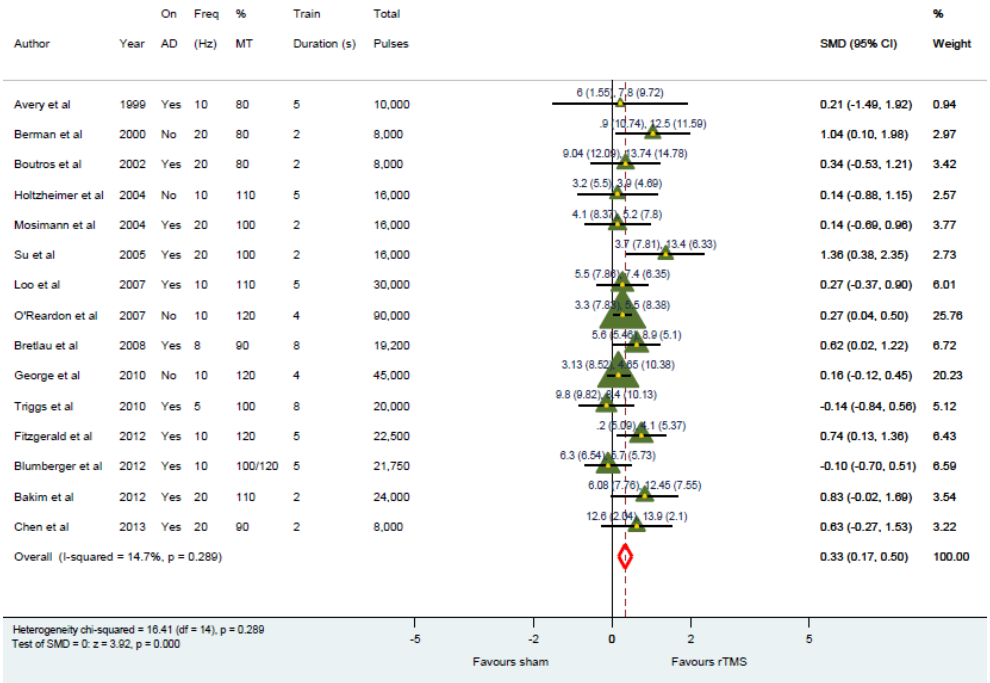

Figure 5: Standardized mean difference: rTMS vs sham (Source: HQO [13])

rTMS vs ECT

Four studies reported depression scores at baseline and at the end of treatment (one study reported mean differences only, without standard deviation data). The weighted mean difference was -5.97 points (95% CI -11.0 to -0.94, p=.020) in favour of ECT. The degree of heterogeneity among studies was high (I^2=72.2%, p=.013). This point value is higher than the 3.5 points, which was defined a priori as clinically important.

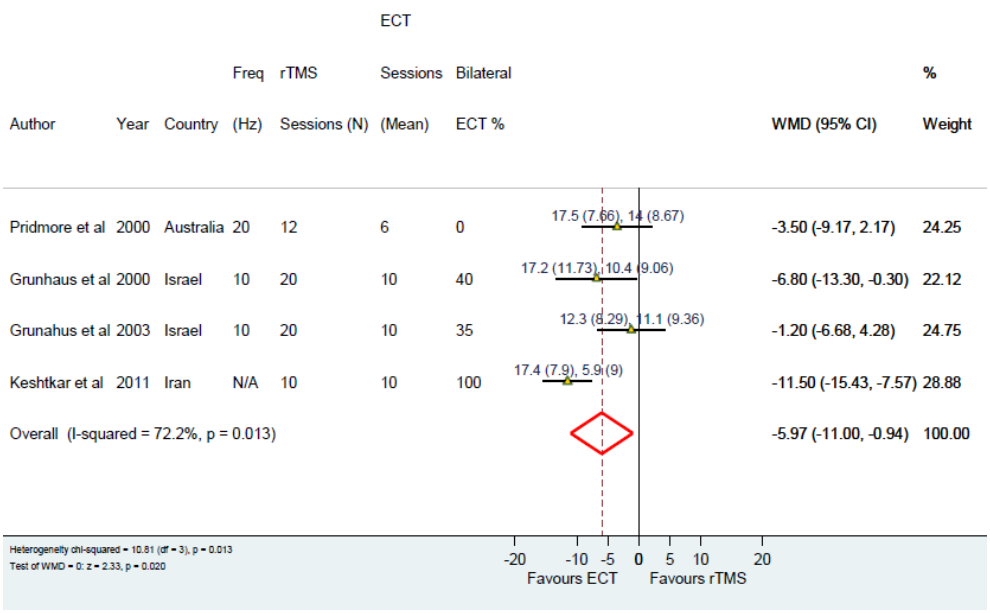

Figure 6: Weighted mean diference: rTMS vs ECT (Source: HQO [13])

The standardized mean deviation was calculated using Cohen's method, the effect size was -0.67 (95% CI -1.23 to -0.10, p=.021) in favour of ECT, which is considered a large effect size. The heterogeneity among studies was high (I^2=70.6%, p=.017).

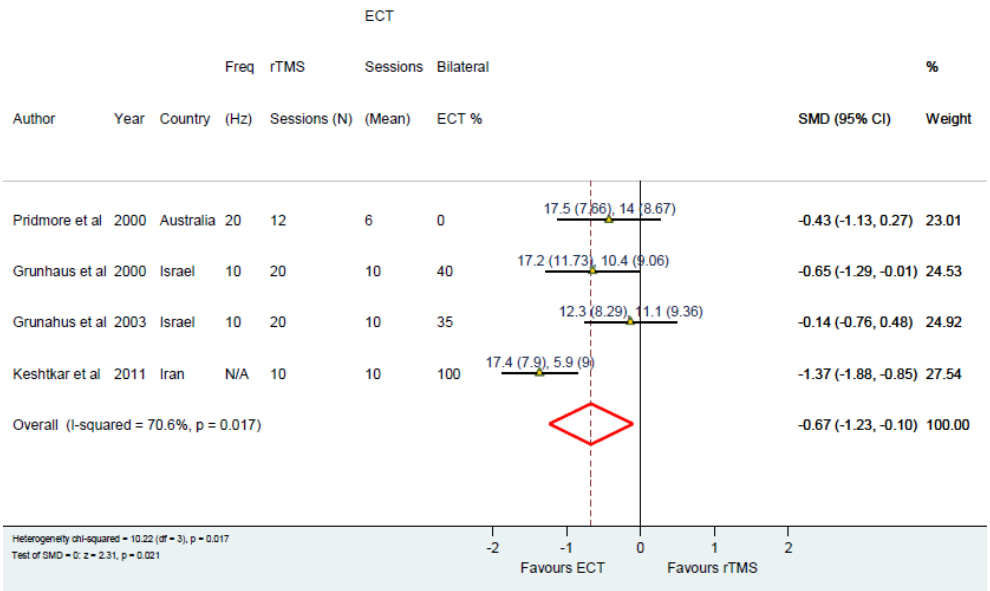

Figure 7: Standardized mean different: rTMS vs ECT (Source: HQO [13])

[D0006] – How does rTMS affect progression (or recurrence) of treatment-resistant major depressive disorder?

rTMS vs sham

Remission rates were reported in the HQO report [13] in 13 studies. The pooled risk ratio has been calculated only for the ones that complied with the safety standards, hence, two studies [56, 57] were excluded from the analysis. The one RCT [14] that was identified in the update of the HQO report also reported on remission. Therefore, we calculated the pooled risk ratio for 12 studies, which was 2.16 (95% CI 1.42-3.29, p=.0003). This pooled estimate suggests that patients may be twice more likely to experience remission with rTMS than with sham. No heterogeneity was observed among the studies (I^2=0.0%, p=.7164). Note that in Fitzgerald 2003 [63], no patients achieved remission in either arm and therefore, it did not contribute to the summary estimate.

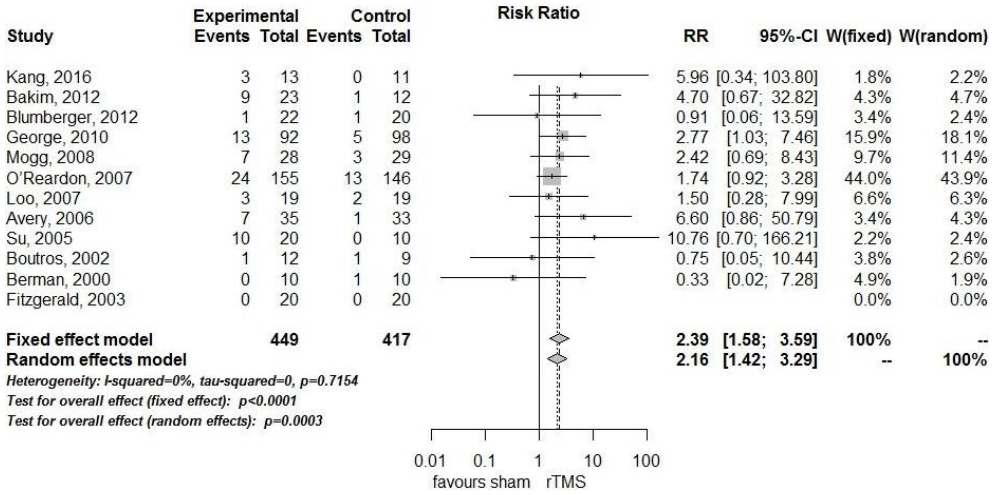

Figure 8: Remission rate at the end of treatment: rTMs vs sham

The risk difference, which, in this case, could be named benefit difference for remission, comparing rTMS with sham was 0.10 (95% CI, 0.03-0.17, p=.0048). That indicates a 10% benefit increase in remission rate favouring active treatment over sham. The heterogeneity among studies was moderate (I^2=58.9%, p=.005). This means that patients treated with active rTMS are more likely to achieve a remission from their disease than the sham group.

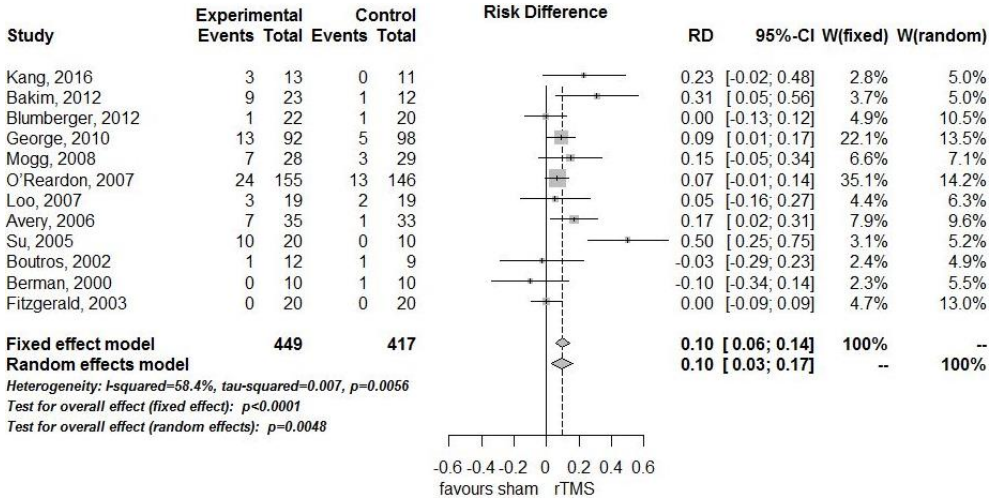

Figure 9: Risk difference for remission rate: rTMS vs sham

Response rates were reported in 20 studies in the HQO report, but only 18 studies complied with the safety standards (two studies [56, 57] were excluded from the meta-analysis). Additionally, the one RCT [14] that was identified in the update of the HQO report also reported on response. Hence, we calculated the pooled risk ratio for response rate across 19 studies, which was 1.82 (95% CI 1.18-2.82, p=.0068). This pooled estimate suggests that patients may be twice more likely to experience treatment response with rTMS than with sham. There was a moderate degree of heterogeneity among studies (I^2=50%, p=.01). The benefit difference for response was 0.13 (95% CI 0.05-0.22, p=.0014) indicating a 13% increase in response rate comparing rTMS with sham. There was a high degree of heterogeneity among studies (I^2=74.1%, p<.0001). Note that in Holtzheimer 2004 [64] and in Fitzgerald 2003 [63], no patients responded to the treatment in either arm, therefore, it did not contribute to the summary estimate.

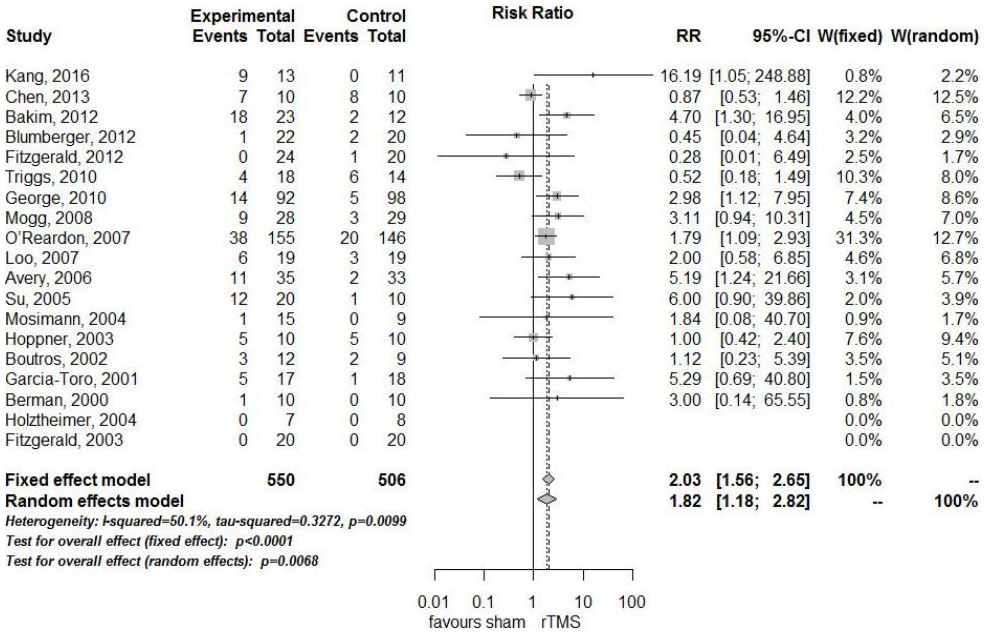

Figure 10: Response rate at the end of treatment: rTMS vs sham

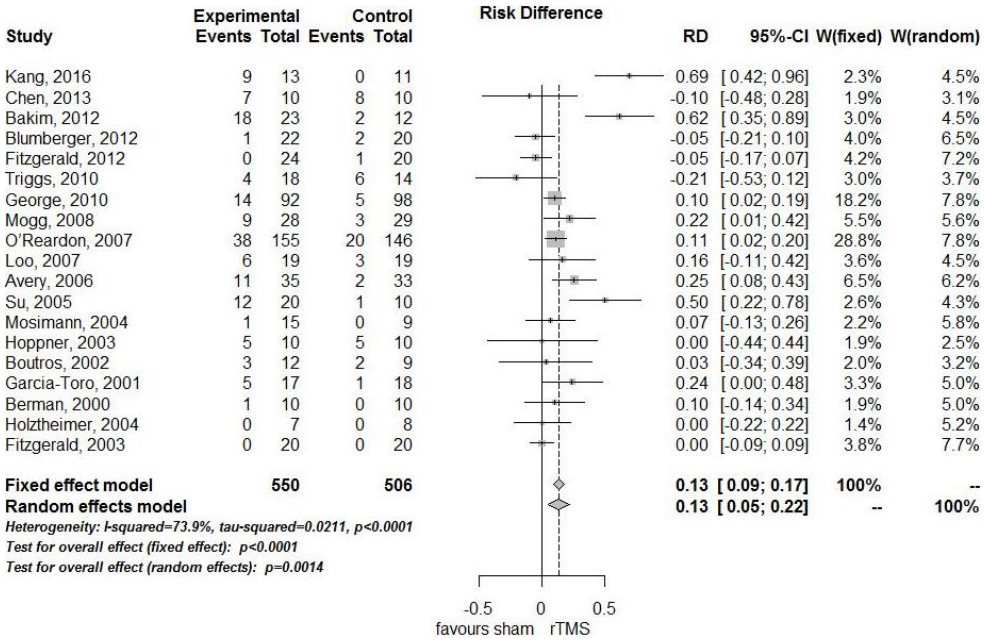

Figure 11: Risk difference for response rate: rTMS vs sham

We conducted a subgroup analysis of the relative risk of response to compare studies that included patients with ≥2 failed trials versus those with ≥1 failed trial, which showed more heterogeneity among studies that included patients with ≥2 failed trials (I^2=62.7%, p=.0013), the results for studies that included patients with ≥1 failed trial were more homogenous (I^2=0%, p=.56). However, these results however must be considered very cautiously. The strength of the evidence is very limited, because although five studies had an inclusion criteria ≥ 1 failed trial, in reality the majority of the included patients had ≥2 failed trials. In O'Reardon more than half of the included patients had more than two failed trials. In George the patients had an average of 1.5 failed research quality adequate treatment trials, which translates into three to six clinical antidepressant medications. In Berman three out of 20 patients had one failed trial (one in the active, two in the sham groups). In Loo and Hoppner there is no information about the rate of patients who failed only one and those who failed more than one trials. Considering the number of patients of these two studies compared to the sum of the five studies it accounts for only 10%. This means that the two groups of studies included very similar patient groups indeed.

rTMS vs ECT

Only three of the six studies that complied with safety standards in the HQO report included data on remission and, therefore, were included in the pooled risk ratio calculation, which was 1.44 (95% CI 0.64-3.23, p=.375) at the end of treatment, favouring ECT. However, these results are not significant. There was a high degree of heterogeneity among studies (I^2=69.1%, p=.039).

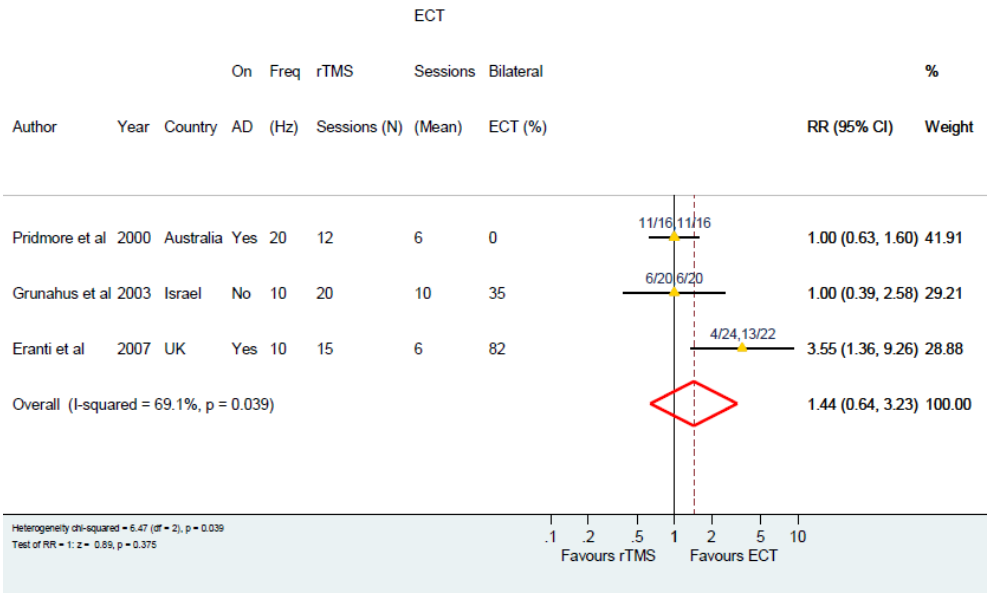

Figure 12: Remission rate: rTMS vs ECT (Source: HQO [13])

Three of the six studies that complied with the safety standards reported on response rate in the HQO report. The pooled risk ratio for response at the end of treatment was 1.72 (95% CI 0.95-3.11, p=.072) favouring ECT. There was again a high degree of heterogeneity among studies (I^2=60.6%, p=.079). While the effect is not statistically significant, this pooled estimate would suggest a higher response with ECT than with rTMS. The benefit increase was 29% (95% CI 0.07-0.5, p=.010) favouring ECT.

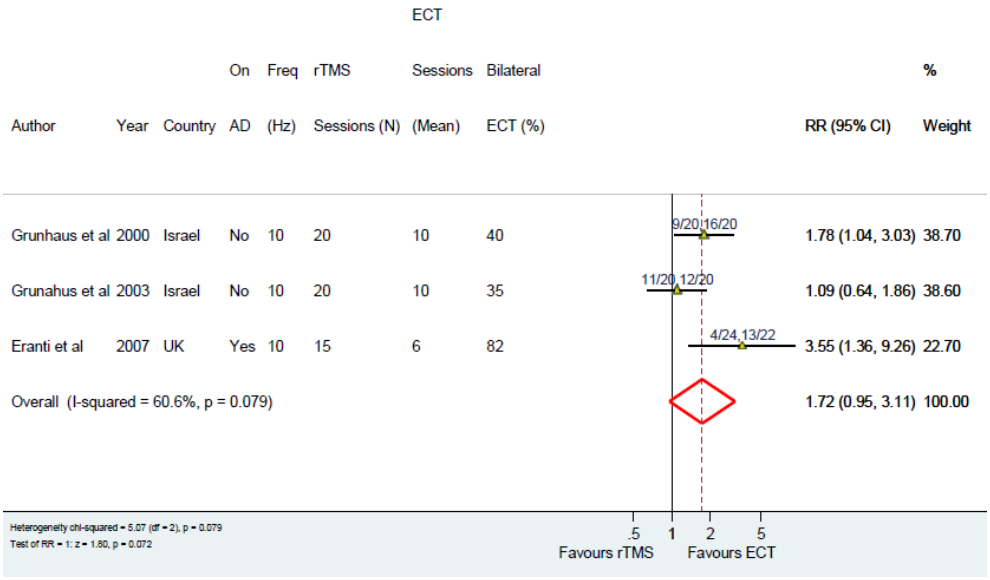

Figure 13: Response rate: rTMS vs ECT (Source: HQO [13])

[D0011] – What is the effect of rTMS on patients' body functions? and

[D0016] – How does the use of rTMS affect activities of daily living?

Only one study [15] assessed changes in performing activities of daily living and patients' body functions within the general QoL assessment measured by the SF-36 tool physical functioning, bodily pain, vitality and role physical subscales. For role physical subscale, the improvement was not statistically significant either at 4- and 6-week or at 6 month time points. The physical functioning improvement was statistically significant from the baseline score of 45.9 (10.5) to 47.3 (9.6) at week 6 (p=0.019) in the intervention group, while from baseline 43.2 (11.3) to 44.6 (10.5) at week 6 (p=0.043) in the sham group. Bodily pain scores improved from baseline 43.5 (9.5) to 44.7 (9.3) at week 4 (p=0.038) and to 45.5 (9.2) at week 6 (p=0.002) in the intervention group. In the sham group the improvement was statistically notnsignificant. Vitality scores also improved from baseline score of 31.8 (6.8) to 35.1 (9.4) at week 4 (p<0.001) and to 36.2 (11.2) at week 6 (p<0.001) in the active group and from baseline 29.9 (5.9) to 32.6 (8.5) at week 4 (p<0.001) and to 33.0 (9.4) at week 6 (p<0.001) in the sham group. The long-term outcomes of 6 months showed no statistically significant improvements in both groups.

Health-related quality of life

[D0012] – What is the effect of rTMS on generic health-related quality of life?

One RCT [15] described QoL outcomes from acute treatment with rTMS. There was a statistically significant improvement favouring rTMS for the SF-36 subscale scores of general health at both the 4- and 6-week time points (from baseline 41.1 (9.8) to 42.4 (9.7) at week 4 (p=0.049), and to 42.6 (10.1) (p=0.047) at week 6). Statistically significant improvement favouring rTMS was also seen in the Q-LES-Q total score at 4-and 6-week time points (from baseline 37.6 (8.2) to 41.3 (10.3) (p<0.001) at week 4 and to 42.4 (12.3) (p<0.001) at week 6). These significant improvments on the SF-36 subscale of general health and the Q-LES-Q favouring rTMS were also reported at the 6-month follow up.

[D0013] – What is the effect of rTMS on disease-specific quality of life?

The same RCT [15] described QoL outcomes from acute treatment with rTMS. There was a statistically significant improvement favouring rTMS for the SF-36 subscale scores of mental health at both the 4- and 6-week time points (from baseline 25.1 (8.7) to 29.3 (11.3) ($p<0.001$) at week 4 and to 30.5 (13.0) ($p<0.001$) at week 6). The improvement on the SF-36 was predominantly evident in the domains of mental health and general health perceptions.

Satisfaction

[D0017] – Were patients satisfied with rTMS?

There were no studies identified that addressed patient satisfaction per se.

5.3 Discussion

The overall quality of the body of evidence is very low for both sham and in ECT controlled studies, which might limit the robustness of our findings.

The methodological limitations of the studies included in this assessment are likely to influence the treatment effect size. First of all, the treatment protocols of rTMS varied among the studies, especially in the sham controlled ones. The HQO report conducted three subgroup analyses of the weighted mean difference of depression scores to investigate the effect of the various treatment parameters like frequency, total pulses, and total sessions on the treatment outcome. The results show that studies that applied a frequency of 20 Hz with shorter train duration had a larger treatment effect than those with 10 or less Hz. This suggests that studies with suboptimal treatment parameters are more likely to result in suboptimal efficacy, although it is still unclear what the most optimal parameters are to reach the best outcome. The safety guidelines recommend a range within which the intervention is delivered most safely, but it is up to the treating physician to decide the exact parameters. In the ECT controlled trials, the heterogeneity among studies can be explained by the variation of treatment parameters used in ECT application (unilateral or bilateral). The HQO report also conducted a subgroup analysis for ECT electrode placement. The subgroup of studies that used bilateral ECT in at least 40% of patients showed larger treatment effect than studies that used only unilateral placement or bilateral in less than 40% of patients.

A further limitation is that most of the included studies used inadequate methods of targeting the DLPFC, i.e. the 5 cm rule, which has been discussed lately and found to be suboptimal in reaching optimal treatment intensity [1, 41, 65].

The definition of remission varied greatly in the studies (from ≤7 to ≤10 using the HDRS-17 and <8 to ≤10 using the HDRS-21). Hence, some studies qualified more patients as remitters than others. The level of treatment resistance was also not uniform across the studies, suggesting that some studies might have included patients with lower severity TRD than others. Change in depression scores, remission and response rates were the primary outcomes assessed and also these were the ones most frequently reported on. A major limitation in the use of mean difference as an outcome is that it is not showing directly if the patient has responded to the treatment.

The sample sizes of the RCTs are small in both the sham and the ECT trials, therefore, it is difficult to draw definitive conclusions about the true level of efficacy. There are four ongoing

studies investigating rTMS compared to sham with the number of enrolled patients ranging from 28 to 168, a size which would not have a significant influence on magnitude of the effect of our findings.

Although the authors of the HQO report collected data if the treatment was delivered as mono- or add-on therapy, they did not conduct a subgroup analysis for this category (16 studies applied rTMS or sham as an add-on therapy and seven as monotherapy). If clinicians get to know the augmentation effect of the intervention, it could further help them in defining the place of the technology in the treatment hierarchy.

Only a few studies provided follow-up data hence we cannot assess the long-term effectiveness and benefits of rTMS. The follow-up ranged from 1 to 6 months. Three rTMS versus sham studies [66-68] reported only on the depression scores, one study [69] reported relapse rate among responders, namely that five patients out of 11 (45.5%) from the rTMS group and one of the two (50%) from the sham group responders relapsed. From the rTMS versus ECT studies, two reported on follow-up data (3 to 6 months). Eranti reported that two of the four (50%) patients relapsed from the remitters in the rTMS and six of twelve (50%) in the ECT group. In Dannon (the follow-up study of Grunhaus 2000), four of the nine responders in the rTMS group and four of the 16 responders in the ECT group relapsed.

Furthermore, patient satisfaction was not measured by any dedicated tool, but some of the studies mentioned that withdrawal (drop-out) occurred due to inconvenience of daily travelling to sessions, inability to attend sessions, attendance perceived to be too stressful, and lack of perceived benefits (although these were only sporadic events). Satisfaction would be a very important outcome as it would show acceptability of the intervention.

The sham controlled studies that were excluded from the meta-analysis based on non-compliance with safety guidelines [56, 57] reported response rates of 25 to 50% in the active groups versus 0% in the sham groups, and both studies reported 33% versus 0% remission rates. The ECT controlled study [61] excluded from the meta-analysis for the same reason reported that 50% of patients responded in the active group and 40% in the sham group, while 10% in the active group and 20% in the sham group achieved remission.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is rTMS in relation to sham stimulation and ECT?
C0002	Are the harms related to dosage or frequency of applying rTMS?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of rTMS?
C0007	Are rTMS, sham stimulation and ECT associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of rTMS, sham stimulation and ECT?

6.2 Results

Included studies

The same secondary studies used in the Clinical Effectiveness domain were assessed for inclusion in the Safety domain. The justification for their exclusion is explained in detail in the chapter on methods. We included 1 systematic review, which was the most recently published systematic review that met our inclusion criteria. The review was updated within the present assessment. The studies screened for their inclusion in the safety analysis were the same as those considered in the Clinical Effectiveness domain, but they did not meet the inclusion criteria for safety as they presented no safety data.

rTMS vs sham

In the updated HQO report [13], 16 studies reported on adverse events. One study provided scores on a side effect scale [66]. One study reported no serious adverse events, three studies did not report on adverse events. Headache and scalp discomfort were the most frequently reported adverse events, while seizures are considered serious adverse event and were reported in 11 studies. Transient impairment of working memory, another serious adverse event was reported in only two studies [68, 70].

rTMS vs ECT

Only one study did not report in any form of adverse events [61]. Only two studies reported on seizure [20, 71], there studies reported on headache [20, 71, 72], one on device-related insomnia [72], one on transient impairment of working memory [20] and two studies used side-effects rating scores [19, 73], but did not report explicitly which side-effects occurred. Only one study reported explicitly that no serious adverse event occurred [20]. No data was reported on other adverse events such as syncope, scalp discomfort and pain, facial twitching, vertigo, induced current circuits in implanted devices, transient hearing loss, transient induction of hypomania, and mild confusion.

Patient safety

[C0008] – How safe is rTMS in relation to sham stimulation and ECT?

rTMs vs sham

The most common side-effect presented in the studies was headache. The rate of headache ranged from 0 to 60% in the rTMS group and 0 to 50% in the sham group. Pain or discomfort of the scalp was also frequent with rates ranging from 4.5% to 78.9% in the rTMS and from 0 to 21% in the sham groups. The rate of gastrointestinal problems ranged from 7% to 22% in the rTMS group and 0 to 22% in the sham group. Eye problems were also common ranging from 5.6% to 21% among rTMS patients and 0 to 1.9% in sham-treated patients. Serious adverse events, including seizures did not occur in any of the 11 studies that reported on this outcome. Transient impairment of working memory, another serious adverse event was reported in only two studies [68, 70] and occurred in five patients (16.7%) in the rTMS group and one patient (4.3%) in the sham group.

rTMS vs ECT

No serious safety concerns were identified. The most common side-effects were headaches in rTMS-treated patients. No adverse events occurred in ECT-treated patients.

[C0002] – Are the harms related to dosage or frequency of applying rTMS?

The currently available evidence is insufficient to address which aspects could affect the frequency and/or severity of harms associated with rTMS.

[C0005] – What are the susceptible patient groups that are more likely to be harmed through the use of rTMS?

No subgroup analysis was performed in the included studies, therefore, there is no data available to answer this assessment element.

[C0007] – Are rTMS, sham stimulation and ECT associated with user-dependent harms?

Effects of a learning curve have not been addressed in any of the studies included for the present safety analysis.

[B0010] – What kind of data/records and/or registry is needed to monitor the use of rTMS, sham stimulation and ECT?

Both for ECT and rTMS use, there is a need for record keeping protocol, recording the adverse events, service level data such as the number of patients treated, the number of treatments, and patient satisfaction. A quality assurance should be done through monitoring the above data, the servicing of the equipment, and the staff training by the facilities providing the technologies.

Table 5: Frequency and severity of adverse events in comparative studies

Adverse events	rTMS vs sham					rTMS vs ECT				
	Studies reporting data	N (%) of rTMS pts with event	N (%) of sham pts with event	% range of event in the included studies rTMS	% range of event in the included studies sham	Studies reporting data	N (%) of rTMS pts with event	N (%) of ECT pts with event	% range of event in the included studies rTMS	% range of event in the included studies ECT
Headache	[17, 58-60, 62, 63, 68, 69, 74-78]	144 (32)	45 (11)	0 – 60	0-50	[20, 71, 72]	9 (12.3)	0	3 – 25	0
Scalp discomfort	[17, 58, 59, 63, 68, 70, 74, 77, 79]	70 (19)	16 (5)	4.5 – 33	0 – 21	NA	NA	NA	NA	NA
Vertigo	[59, 62, 63, 67-69]	7 (3.3)	8 (3.9)	0 – 16.7	0 – 14	NA	NA	NA	NA	NA
Seizure	[17, 56-58, 67, 69, 74, 76, 77, 79, 80]	0	0	0	0	[20, 71]	1 (1.9)	0	0 – 5	0
Gastrointestinal problems	[17, 59, 62, 68, 70, 77]	25 (8)	7 (2.4)	5 – 22	0 – 22	NA	NA	NA	NA	NA
Eye problems	[17, 62, 68, 77]	15 (7.2)	3 (1.6)	5.6 – 21	0 – 1.9	NA	NA	NA	NA	NA
Face twitching	[17, 59, 68, 77]	15 (5.3)	6 (2.2)	0 – 20.6	0 – 3.2	NA	NA	NA	NA	NA
Insomnia	[59, 68, 74]	9 (6.7)	11 (8.2)	4.5 – 7.6	0 – 10	[72]	2 (10)	0	0	0
Syncope	[59, 68]	10 (9)	6 (5.4)	5 – 27.8	4 – 14	NA	NA	NA	NA	NA
Hypomania	[60, 77]	2 (5.1)	0	0	0	NA	NA	NA	NA	NA
Cognitive impairment	[68, 70]	5 (16.7)	1 (4.3)	0 – 41.7	0 – 7	[20]	0	0	0	0
Death	[17]	0	0	0	0	NA	NA	NA	NA	NA

Abbreviations: ECT electroconvulsive therapy, N number, pts patients, rTMS repetitive transcranial magnetic stimulation

6.3 Discussion

The body of evidence indicates that rTMS is generally safe and well-tolerated. The most serious adverse device effects are seizure and transient impairment of working memory.

The risk during treatment course is less than 0.5 percent when safety guidelines regarding patient selection and stimulation parameters are followed. As described in the safety guideline [2], if seizures happen, they are usually self-limited, require no medications, and do not recur. The studies did not address the issue of which patient groups are more likely to be harmed by using the technology. According to the evidence-based clinical decision support guidance by Holtzheimer and colleagues, the factors that might increase the risk of seizures include patient factors as personal and family history of epilepsy, pre-existing neurologic disorder, medications that lower seizure threshold, recent discontinuation of alcohol, benzodiazepines or anticonvulsants, sleep deprivation; and technical factors like higher frequency, increased intensity, and shorter intertrain interval [3]. These technical parameters are defined in the safety guidelines and should not be exceeded. Regarding patient factors, many studies defined them as exclusion criteria.

The sham controlled studies that were excluded from the meta-analysis based on non-compliance with safety guidelines reported very vaguely on adverse events (both studies [56, 57] reported a total number of patients with headache, not specifying from which groups). The ECT controlled study [61] excluded from the meta-analysis for the same reason did not report on adverse events at all.

The most serious limitation of the included studies comparing rTMS and ECT is that only some of them reported on adverse events and only one study [19] measured cognitive impairment, which is the most common adverse event in ECT therapy.

Broadly, the included studies that compare rTMS and ECT were of low quality, most of them had a high risk of bias in the blinding domain for patients and medical staff as well as in outcome assessors in some cases. However, given the nature of the intervention, blinding is not possible, because ECT would require general anaesthesia, while rTMS not. The sham controlled studies were of very low to low quality, most of them having a combination of unclear and low risk of bias, and a few having high risk of bias. In these studies, blinding was the area where the studies were often lacking clarity. Methods of random sequence generation and allocation concealment were largely unclear; however, this could have been due to a lack of detail rather than an area of bias. The number of events and number of patients were both in the sham and in the ECT controlled studies very low.

7 REFERENCES

[1] Lefaucheur JP, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clinical Neurophysiology. 2014;125:2150-206.

[2] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009(12):2008–39.

[3] Holtzheimer P. Unipolar depression in adults: Treatment with transcranial magnetic stimulation (TMS). In: Roy-Byrne P, Solomon D, editors. UpToDate. Aug 13, 2015: UpToDate; 2015.

[4] Hardy S, Bastick L, O'Neill-Kerr A, Sabesan P, Lankappa S, Palaniyappan L. Transcranial magnetic stimulation in clinical practice. Advances in Psychiatric Treatment. 2016;22(6):373-9.

[5] Mag&More GmbH. Evidence submission templates to support production of core HTA information and rapid assessments: Medical devices evidence submission template short version 2017.

[6] Milev RV, Giacobbe P, Kennedy SH, Blumberger DM, Daskalakis ZJ, Downar J, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments. Can J Psychiatry. 2016;61(9):561-75.

[7] Greenhalgh J, Knight C, Hind D, Beverley C, Walters S. Electroconvulsive therapy (ECT) for depressive illness, schizophrenia, catatonia and mania. NICE/National Institute for Health and Care Excellence,; 2002 [05.01.2017]; Available from: https://www.nice.org.uk/guidance/ta59/documents/final-assessment-report-electroconvulsive-therapy-ect-for-depressive-illness-schizophrenia-catatonia-and-mania2.

[8] Cme Institute of Physicians Postgraduate Press Inc. Transcranial magnetic stimulation: potential new treatment for resistant depression. Journal of Clinical Psychiatry. 2007;68(2):315-30.

[9] Thase M. Unipolar treatment resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis. In: Roy-Byrne P, Solomon D, editors. UptoDate. Dec 30, 2015: UptoDate; 2015.

[10] WHO/World Health Organization. The world health report 2001. Mental health: new understanding, new hope. Geneva, Switzerland 2001.

[11] Wani A, Trevino K, Marnell P, Husain MM. Advances in brain stimulation for depression. Ann Clin Psychiatry. 2013;25(3):217-24.

[12] Nemeroff CB. Prevalence and management of treatment-resistant depression. Journal of Clinical Psychiatry. 2007;68(SUPPL. 8):17-25.

[13] Health Quality O. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Ont Health Technol Assess Ser. 2016;16(5):1-66.

[14] Kang JI, Lee H, Jhung K, Kim KR, An SK, Yoon KJ, et al. Frontostriatal connectivity changes in major depressive disorder after repetitive transcranial magnetic stimulation: A randomized Sham-Controlled study. Journal of Clinical Psychiatry. 2016;77(9):e1137-e43.

[15] Solvason HB, Husain M, Fitzgerald PB, Rosenquist P, McCall WV, Kimball J, et al. Improvement in quality of life with left prefrontal transcranial magnetic stimulation in patients with pharmacoresistant major depression: acute and six month outcomes. Brain Stimulation. 2014;7(2):219-25.

[16] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J ea. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology. 2011;64:383-94.

[17] O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry. 2007;62(11):1208-16. Epub 2007/06/19.

[18] Dannon PN, Dolberg OT, Schreiber S, Grunhaus L. Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals – preliminary report. Biol Psychiatry. 2002;51(8):687-90. Epub 2002/04/17.

[19] Eranti S, Mogg A, Pluck G, Landau S, Purvis R, Brown RG, et al. A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. Am J Psychiatry. 2007;164(1):73-81. Epub 2007/01/05.

[20] Keshtkar M, Ghanizadeh A, Firoozabadi A. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for the treatment of major depressive disorder, a randomized controlled clinical trial. J Ect. 2011;27(4):310-4. Epub 2011/11/15.

[21] APA/American Psychiatric Association, Gelenberg AJ, Freeman MP, Markowitz JC, Rosenbaum JF, Thase ME, et al. Practice guideline for the treatment of patients with major depressive disorder. In: Reus VI, DePaulo JR, Fawcett JA, Schneck CD, Silbersweig DA, editors.: American Psychiatric Association (APA); 2010.

[22] Leitliniengruppe Unipolare Depression, DGPPN, BÄK, KBV, AWMF, AkdÄ, et al. S3-Leitlinie/ Nationale VersorgungsLeitlinie Unipolare Depression – Langfassung, 2. Auflage. Version 4. 2015.

[23] NICE/National Institute for Health and Care Excellence. Repetitive transcranial magnetic stimulation for depression. Interventional procedure guidance 542. 2015.

[24] WSFBP/World Federation of Societies of Biological Psychiatry. Guidelines for Biological Treatment of Unipolar Depressive Disorders, Part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders. In: Task Force on Unipolar Depressive Disorders, editor.: WSFBP; 2013.

[25] Malhi G, Bassett D, Boyce P, Bryant R, Fitzgerald P, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Australian and New Zealand Journal of Psychiatry. 2015;49(12):1-185.

[26] EUnetHTA. Guideline. Therapeutic medical devices. EUnetHTA; 2015.

[27] EUnetHTA. Guideline. Endpoints used for Relative Effectiveness Assessment: Clinical endpoints. EUnetHTA; 2015.

[28] EUnetHTA. Guideline. Comparators & comparisons. Criteria for the choice of the most appropriate comparator(s). Summary of current policies and best practice recommendations. EUnetHTA; 2015.

[29] R: a language and environment for statistical computing [database on the Internet]. R Foundation for Statistical Computing, Vienna. 2015.

[30] Meta: general package for meta-analysis. R package version 4.3-2 [database on the Internet]. 2015.

[31] George MS, Taylor JJ, Short EB. The expanding evidence base for rTMS treatment of depression. Curr Opin Psychiatry. 2013;26(1):13-8.

[32] Mag&More GmbH. The PowerMAG stimulators. 2017 [03.01.2017]; Available from: http://www.magandmore.com/en/products/rtms.html.

[33] Magstim. rTMS for Major Depressive Disorder (MDD). 2017 [03.01.2017]; Available from: http://www.magstim.com/clinical-area/rtms-for-major-depressive-disorder-mdd.

[34] Magventure. MagPro magnetic stimulators. 2017 [03.01.2017]; Available from: http://www.magventure.com/en-gb/Products/MagPro-magnetic-stimulators.

[35] Neuronetics. NeuroStar TMS System Technical Data Sheet. 2017 [03.01.2017]; Available from: https://neurostar.com/wp-content/uploads/80-50101-002-NeuroStar-TMS-System-Version-1.7-Technical-Data-Sheet.pdf.

[36] Neurosoft. Neurosoft CE mark certificate. 2017 [03.01.2017]; Available from: http://www.neurosoft.ru/eng/utils/view.aspx?back=/eng/diploma/index.aspx&pre=../diploma/neuro-ms_ce/img&current=1&count=4&post=b.gif.

[37] Neurosoft. Neuro-MS. 2017 [03.01.2017]; Available from: http://www.neurosoft.ru/eng/product/neuro-ms/.

[38] European Commission/DG Health and Consumer. Medical devices: guidance document – classification of medical devices. In: Directorate B; Unit B2 “Cosmetics and medical devices”, editor.2010.

[39] Duecker F, Sack AT. Rethinking the role of sham TMS. Front Psychol 2015;6:210. Epub 2015 Feb 26.

[40] FDA/Food and Drug Administration. (510)k summary of the Neurostar TMS System 2008 [03.01.2017]; Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf8/K083538.pdf.

[41] Daskalakis ZJ, Levinson AJ, Fitzgerald PB. Repetitive transcranial magnetic stimulation for major depressive disorder: a review. Can J Psychiatry. 2008;53(9):555-66.

[42] Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS. The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder. Brain Stimulation. 2016;9(3):336-46.

[43] Nordenskjold A, Martensson B, Pettersson A, Heintz E, Landen M. Effects of Hesel-coil deep transcranial magnetic stimulation for depression – a systematic review. Nord J Psychiatry. 2016;70(7):492-7.

[44] Kornstein S, Schneider R. Clinical features of treatment-resistant depression Journal of Clinical Psychiatry. 2001;62(suppl6):18-25.

[45] Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. Psychiatric Services. 2014;65(8):977-87.

[46] WHO/World Health Organization. The Global Burden of Disease: 2004 Update. Geneva: WHO; 2004.

[47] Olchanski N, McInnis Myers M, Halseth M, Cyr P, Bockstedt L, Goss T, et al. The economic burden of treatment-resistant depression. Clin Ther 2013;35(4):512-22. Epub 2013 Mar 13.

[48] Sackeim H, Prudic J, Devanand D, Decina P, Kerr B, Malitz S. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electro-convulsive therapy in major depression. J Clin Psychopharmacol 1990;10(2):96-104.

[49] Oquendo M, Malone K, Ellis S, Sackeim H, Mann J. Inadequacy of antidepressant treatment for patients with major depression who are at risk for suicidal behavior. Am J Psychiatry 1999;156(2):190-4.

[50] Fekadu A, Wooderson S, Donaldson C, Markopoulou K, Masterson B, Poon L, et al. A multidimensional tool to quantify treatment resistance in depression: the Maudsley staging method. J Clin Psychiatry 2009;70(2). Epub 2009 Jan 27.

[51] Thase M, Connolly R. Unipolar depression in adults: Treatment of resistant depression. In: Roy-Byrne P, Solomon D, editors. UpToDate. Jul 20, 2016: UpToDate; 2016.

[52] Al-Harbi KS. Treatment-resistant depression: therapeutic trends, challenges, and future directions. Patient preference and adherence. 2012;6:369-88.

[53] Thase M. Unipolar depression in adults: Management of highly resistant (refractory) depression. In: Roy-Byrne P, Connolly R, editors. UpToDate. Dec 30, 20152015.

[54] Kasper S, Lehofer M, Doering S, Geretsegger C, Frey R, Haring C, et al. Depression – Medikamentöse Therapie. CliniCum neuropsy Sonderausgabe. 2012 (November 2012).

[55] Wijeratne C, Sachdev P. Treatment-resistant depression: critique of current approaches. Australian and New Zealand Journal of Psychiatry. 2008;42:751-62.

[56] Padberg F, Zwanzger P, Keck ME, Kathmann N, Mikhaiel P, Ella R, et al. Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. Neuropsychopharmacology. 2002;27(4):638-45. Epub 2002/10/16.

[57] Stern WM, Tormos JM, Press DZ, Pearlman C, Pascual-Leone A. Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: a double-blind, randomized, placebo-controlled trial. The Journal of neuropsychiatry and clinical neurosciences. 2007;19(2):179-86. Epub 2007/04/14.

[58] Bakim B, Uzun UE, Karamustafalioglu O, Ozcelik B, Alpak G, Tankaya O, et al. The combination of antidepressant drug therapy and high-frequency repetitive transcranial magnetic stimulation in medication-resistant depression. Klinik Psikofarmakoloji Bulteni. 2012;22(3):244-53.

[59] George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Archives of general psychiatry. 2010;67(5):507-16. Epub 2010/05/05.

[60] Su TP, Huang CC, Wei IH. Add-on rTMS for medication-resistant depression: a randomized, double-blind, sham-controlled trial in Chinese patients. J Clin Psychiatry. 2005;66(7):930-7. Epub 2005/07/15.

[61] Rosa MA, Gattaz WF, Pascual-Leone A, Fregni F, Rosa MO, Rumi DO, et al. Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. The international journal of neuropsychopharmacology. 2006;9(6):667-76. Epub 2006/08/23.

[62] Mosimann UP, Schmitt W, Greenberg BD, Kosel M, Muri RM, Berkhoff M, et al. Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. Psychiatry Res. 2004;126(2):123-33. Epub 2004/05/05.

[63] Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, De Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. Archives of general psychiatry. 2003;60(10):1002-8. Epub 2003/10/15.

[64] Holtzheimer PE, 3rd, Russo J, Claypoole KH, Roy-Byrne P, Avery DH. Shorter duration of depressive episode may predict response to repetitive transcranial magnetic stimulation. Depress Anxiety. 2004;19(1):24-30. Epub 2004/02/24.

[65] Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of standard coil positioning by neuronavigation. Biological Psychiatry. 2011;50:58-61.

[66] Bretlau LG, Lunde M, Lindberg L, Unden M, Dissing S, Bech P. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. Pharmacopsychiatry. 2008;41(2):41-7. Epub 2008/03/04.

[67] Mogg A, Pluck G, Eranti SV, Landau S, Purvis R, Brown RG, et al. A randomized controlled trial with 4-month follow-up of adjunctive repetitive transcranial magnetic stimulation of the left prefrontal cortex for depression. Psychol Med. 2008;38(3):323-33. Epub 2007/10/16.

[68] Triggs WJ, Ricciuti N, Ward HE, Cheng J, Bowers D, Goodman WK, et al. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: a randomized, sham-controlled trial. Psychiatry Res. 2010;178(3):467-74. Epub 2010/07/21.

[69] Avery DH, Holtzheimer PE, 3rd, Fawaz W, Russo J, Neumaier J, Dunner DL, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. Biol Psychiatry. 2006;59(2):187-94. Epub 2005/09/06.

[70] Boutros NN, Gueorguieva R, Hoffman RE, Oren DA, Feingold A, Berman RM. Lack of a therapeutic effect of a 2-week sub-threshold transcranial magnetic stimulation course for treatment-resistant depression. Psychiatry Res. 2002;113(3):245-54. Epub 2003/02/01.

[71] Grunhaus L, Dannon PN, Schreiber S, Dolberg OH, Amiaz R, Ziv R, et al. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. Biol Psychiatry. 2000;47(4):314-24. Epub 2000/02/25.

[72] Grunhaus L, Schreiber S, Dolberg OT, Polak D, Dannon PN. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. Biol Psychiatry. 2003;53(4):324-31. Epub 2003/02/15.

[73] Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. The international journal of neuropsychopharmacology. 2000;3(2):129-34. Epub 2001/05/10.

[74] Blumberger DM, Mulsant BH, Fitzgerald PB, Rajji TK, Ravindran AV, Young LT, et al. A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. World J Biol Psychiatry. 2012;13(6):423-35. Epub 2011/07/09.

[75] Garcia-Toro M, Mayol A, Arnillas H, Capllonch I, Ibarra O, Crespi M, et al. Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. J Affect Disord. 2001;64(2-3):271-5. Epub 2001/04/21.

[76] Loo C, Mitchell P, Sachdev P, McDarmont B, Parker G, Gandevia S. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. Am J Psychiatry. 1999;156(6):946-8. Epub 1999/06/09.

[77] Loo CK, Mitchell PB, McFarquhar TF, Malhi GS, Sachdev PS. A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. Psychol Med. 2007;37(3):341-9. Epub 2006/12/21.

[78] Berman RM, Narasimhan M, Sanacora G, Miano AP, Hoffman RE, Hu XS, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. Biol Psychiatry. 2000;47(4):332-7. Epub 2000/02/25.

[79] Avery DH, Claypoole K, Robinson L, Neumaier JF, Dunner DL, Scheele L, et al. Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. The Journal of nervous and mental disease. 1999;187(2):114-7. Epub 1999/03/06.

[80] Fitzgerald PB, Hoy KE, Herring SE, McQueen S, Peachey AV, Segrave RA, et al. A double blind randomized trial of unilateral left and bilateral prefrontal cortex transcranial magnetic stimulation in treatment resistant major depression. J Affect Disord. 2012;139(2):193-8. Epub 2012/03/09.

[81] Ministerio de Sanidad, Servicios Sociales e Igualdad. Guía de Práctica Clínica sobre el Manejo de la Depresión en el Adulto. In: Agencia de Evaluación de Tecnologías Sanitarias de Galicia (avalia-t), editor.2014.

[82] Lefaucheur J-P, André-Obadiac N, Poulete E, H. Devanneg H, Haffenj E, Londerol A, et al. French guidelines on the use of repetitive transcranial magnetic stimulation (rTMS): Safety and therapeutic indications. Clinical Neurophysiology. 2011;41(5-6):221-95.

[83] Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychological Medicine. 2014;44(2):225-39.

[84] Berlim MT, Van den Eynde F, Daskalakis ZJ. High-frequency repetitive transcranial magnetic stimulation accelerates and enhances the clinical response to antidepressants in major depression: a meta-analysis of randomized, double-blind, and sham-controlled trials. Journal of Clinical Psychiatry. 2013;74(2):e122-9.

[85] Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, et al. Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis. JAMA Psychiatry. 2016.

[86] Gaynes BN, Lloyd SW, Lux L, Gartlehner G, Hansen RA, Brode S, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. Journal of Clinical Psychiatry. 2014;75(5):477-89; quiz 89.

[87] Hovington CL, McGirr A, Lepage M, Berlim MT. Repetitive transcranial magnetic stimulation (rTMS) for treating major depression and schizophrenia: a systematic review of recent meta-analyses. Ann Med. 2013;45(4):308-21.

[88] Kedzior KK, Azorina V, Reitz SK. More female patients and fewer stimuli per session are associated with the short-term antidepressant properties of repetitive transcranial magnetic stimulation (rTMS): a meta-analysis of 54 sham-controlled studies published between 1997-2013. Neuropsychiatr. 2014;10:727-56.

[89] Kedzior KK, Reitz SK. Short-term efficacy of repetitive transcranial magnetic stimulation (rTMS) in depression- reanalysis of data from meta-analyses up to 2010. BMC Psychol. 2014;2(1):39.

[90] Kedzior KK, Reitz SK, Azorina V, Loo C. Durability of the antidepressant effect of the high-frequency repetitive transcranial magnetic stimulation (rTMS) In the absence of maintenance treatment in major depression: a systematic review and meta-analysis of 16 double-blind, randomized, sham-controlled trials. Depress Anxiety. 2015;32(3):193-203.

[91] Lepping P, Schonfeldt-Lecuona C, Sambhi RS, Lanka SVN, Lane S, Whittington R, et al. A systematic review of the clinical relevance of repetitive transcranial magnetic stimulation. Acta Psychiatrica Scandinavica. 2014;130(5):326-41.

[92] Liu B, Zhang Y, Zhang L, Li L. Repetitive transcranial magnetic stimulation as an augmentative strategy for treatment-resistant depression, a meta-analysis of randomized, double-blind and sham-controlled study. BMC Psychiatry. 2014;14:342.

[93] Leggett LE, Soril LJJ, Coward S, Lorenzetti DL, MacKean G, Clement FM. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression in Adult and Youth Populations: A Systematic Literature Review and Meta-Analysis. Prim Care Companion CNS Disord. 2015;17(6).

[94] Leggett LE, Coward S, Soril LJJ, MacKean G, Lorenzetti DL, Clement FM. Repetitive transcranial magnetic stimulation for treatment resistant depression. In: Health Technology Assessment Unit UoC, editor.: University of Calgary,; 2014.

[95] Serafini G, Pompili M, Belvederi Murri M, Respino M, Ghio L, Girardi P, et al. The effects of repetitive transcranial magnetic stimulation on cognitive performance in treatment-resistant depression. A systematic review. Neuropsychobiology. 2015;71(3):125-39.

[96] Berlim MT, Van den Eynde F, Daskalakis ZJ. Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. Depress Anxiety. 2013;30(7):614-23.

[97] Micallef-Trigona B. Comparing the effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in the treatment of depression: a systematic review and meta-analysis. Depress Res Treat. 2014;2014:135049.

[98] Vallejo-Torres L, Castilla I, Gonzalez N, Hunter R, Serrano-Perez P, Perestelo-Perez L. Cost-effectiveness of electroconvulsive therapy compared to repetitive transcranial magnetic stimulation for treatment-resistant severe depression: a decision model. Psychological Medicine. 2015;45(7):1459-70.

[99] Xie J, Chen J, Wei Q. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a meta-analysis of stimulus parameter effects. Neurol Res. 2013;35(10):1084-91.

[100] Chen J-J, Zhao L-B, Liu Y-Y, Fan S-H, Xie P. Comparative efficacy and acceptability of electroconvulsive therapy versus repetitive transcranial magnetic stimulation for major depression: A systematic review and multiple-treatments meta-analysis. Behavioural Brain Research. 2017;320:30-6.

[101] Ren J, Li H, Palaniyappan L, Liu H, Wang J, Li C, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2014;51:181-9.

[102] Chen SJ, Chang CH, Tsai HC, Chen ST, Lin C. Superior antidepressant effect occurring 1 month after rTMS: add-on rTMS for subjects with medication-resistant depression. Neuropsychiatr Dis Treat. 2013;9:397-401. Epub 2013/04/12.

[103] Höppner J, Schulz M, Irmisch G, Mau R, Schläfke D, Richter J. Antidepressant efficacy of two different rTMS procedures: High frequency over left versus low frequency over right prefrontal cortex compared with sham stimulation. European Archives of Psychiatry and Clinical Neuroscience. 2003;253(2):103-9.

[104] FDA/Food and Drug Administration. 510(k) premarket notification of the Rapid2 Therapy System. 2015 [02.02.2017]; Available from: https://www.accessdata.fda.gov/cdrh_docs/pdf14/K143531.pdf.

[105] FDA/Food and Drug Administration. 510(k) premarket notification of the MagVita TMS Therapy System. 2015 [03.01.2017]; Available from: http://www.accessdata.fda.gov/cdrh_docs/pdf15/k150641.pdf.

[106] Magstim. Magstim Rapid2, Magstim Super Rapid2. 2017 [02.02.2017]; Available from: http://www.magstim.com/product/17/magstim-rapid2, http://www.magstim.com/product/19/magstim-super-rapid-2-plus-1.

[107] BMI Research. NeuroStar TMS given green light in Europe. 2012 [03.01.2017]; Available from: http://www.bmiresearch.com/articles/neurostar-tms-given-green-light-in-europe.

[108] Mag&More GmbH. Combining EEG and rTMS. Advanced Solutions for rTMS Applications. 2011; Available from: http://www.magandmore.com/Downloads/120123combiningeeg&tms.pdf.

[109] TGA/Therapeutic Goods Administration. Neurostar TMS Therapy System – Transcranial magnetic stimulation system. 2014 [02.02.2017]; Available from: https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=231835&agid=%28PrintDetailsPublic%29&actionid=1.

[110] Perestelo-Pérez L, Rivero-Santana A, García-Pérez L, Álvarez-Pérez Y, Castellano-Fuentes C, Toledo-Chávarri A, et al. Indicaciones, seguridad, efectividad y coste-efectividad de la estimulación cerebral no invasiva en el tratamiento de los trastornos mentales. Ministerio de Sanidad, Servicios Sociales e Igualdad. Servicio de Evaluación del Servicio Canario de la Salud; 2016.

[111] Morvai S, Nagy A, Kovács A, Móré CE, Berecz R, Frecska E. Unanswered questions in the transcranial magnetic stimulation treatment of patients with depression. Ideggyogyaszati Szemle. 2016;69(1-2):4-11.

[112] APA/American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. In: Masson, editor. Barcelona 2003.

APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

Search strategy for SRs

Medline via Ovid

Database: Ovid MEDLINE(R) Epub Ahead of Print <December 29, 2016>, Ovid MEDLINE(R) <1946 to December Week 1 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 29, 2016>, Ovid MEDLINE(R) Daily Update <December 07, 2016>	
1	exp Depressive Disorder, Major/(28225)
2	((major or severe) adj3 depress*).ti,ab. (51492)
3	exp Depressive Disorder, Treatment-Resistant/(771)
4	*Depressive Disorder/th [Therapy] (6771)
5	*Depression/th [Therapy] (6904)
6	1 or 2 or 3 or 4 or 5 (72016)
7	exp Transcranial Magnetic Stimulation/(10226)
8	((repetiti* or repeat*) adj3 (Transcrani* adj3 Magnet* Stimul*)).ti,ab. (3774)
9	rTMS.ti,ab. (3698)
10	7 or 8 or 9 (11420)
11	6 and 10 (1102)
12	limit 11 to (meta analysis or systematic reviews) (121)
13	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or “research synthesis” or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not “psycinfo database”) or pubmed or scopus or “sociological abstracts” or “web of science”).ab. or (“cochrane database of systematic reviews” or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/or Meta-Analysis.pt. (340943)
14	11 and 13 (152)
15	12 or 14 (170)
16	remove duplicates from 15 (146)
30.12.2016	

Embase

No.	Query Results	Results	Date
#13.	‘major depression’/exp OR ((major OR severe) NEAR/1 depress*):ti,ab OR ‘treatment resistant depression’/exp OR ‘depression’/mj/dm_th AND (‘transcranial magnetic stimulation’/exp OR ((repetiti* OR repeat*) NEAR/3 (transcrani* OR magnet* OR stimul*)):ti,ab OR rtms:ti,ab) AND (‘meta analysis’/de OR ‘meta analysis (topic)’/de OR ‘systematic review’/de)	182	30 Dec 2016
#12.	‘major depression’/exp OR ((major OR severe) NEAR/1 depress*):ti,ab OR ‘treatment resistant depression’/exp OR ‘depression’/mj/dm_th AND (‘transcranial magnetic stimulation’/exp OR ((repetiti* OR repeat*) NEAR/3 (transcrani* OR magnet* OR stimul*)):ti,ab OR rtms:ti,ab)	1,870	30 Dec 2016

#11.	'major depression'/exp OR ((major OR severe) NEAR/1 depress*):ti,ab OR 'treatment resistant depression'/exp OR 'depression'/mj/dm_th AND ('transcranial magnetic stimulation'/exp OR ((repetiti* OR repeat*) NEAR/3 (transcrani* OR magnet* OR stimul*)):ti,ab OR rtms:ti,ab) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim)	146	30 Dec 2016
#10.	'major depression'/exp OR ((major OR severe) NEAR/1 depress*):ti,ab OR 'treatment resistant depression'/exp OR 'depression'/mj/dm_th AND ('transcranial magnetic stimulation'/exp OR ((repetiti* OR repeat*) NEAR/3 (transcrani* OR magnet* OR stimul*)):ti,ab OR rtms:ti,ab)	1,870	30 Dec 2016
#9.	'transcranial magnetic stimulation'/exp OR ((repetiti* OR repeat*) NEAR/3 (transcrani* OR magnet* OR stimul*)):ti,ab OR rtms:ti,ab	31,969	30 Dec 2016
#8.	rtms:ti,ab	4,758	30 Dec 2016
#7.	((repetiti* OR repeat*) NEAR/3 (transcrani* OR magnet* OR stimul*)):ti,ab	18,884	30 Dec 2016
#6.	'transcranial magnetic stimulation'/exp	17,310	30 Dec 2016
#5.	'major depression'/exp OR ((major OR severe) NEAR/1 depress*):ti,ab OR 'treatment resistant depression'/exp OR 'depression'/mj/dm_th	85,145	30 Dec 2016
#4.	'depression'/mj/dm_th	15,872	30 Dec 2016
#3.	'treatment resistant depression'/exp	1,464	30 Dec 2016
#2.	((major OR severe) NEAR/1 depress*):ti,ab	54,691	30 Dec 2016
#1.	'major depression'/exp	48,114	30 Dec 2016

CRD

#### rTMS for TRD	
Search Date: 30.12.2016	
1	MeSH DESCRIPTOR Depressive Disorder, Major EXPLODE ALL TREES
2	((major OR severe) NEAR depress*)
3	MeSH DESCRIPTOR Depressive Disorder, Treatment-Resistant EXPLODE ALL TREES
4	MeSH DESCRIPTOR depressive disorder EXPLODE ALL TREES WITH QUALIFIER TH
5	MeSH DESCRIPTOR depression EXPLODE ALL TREES WITH QUALIFIER TH
6	#1 OR #2 OR #3 OR #4 OR #5
7	MeSH DESCRIPTOR Transcranial Magnetic Stimulation EXPLODE ALL TREES
8	((repetiti* OR repeat*) NEAR (Transcrani* OR Magnet* OR Stimul*))
9	(rTMS)
10	#7 OR #8 OR #9
11	#6 AND #10
46 Hits	

Cochrane database

Search Name: **rTMS for TRD**	
Last Saved: 30/12/2016 16:16:23.558	
ID	Search
#1	MeSH descriptor: [Depressive Disorder, Major] explode all trees
#2	(major or severe) near depress*:ti,ab,kw (Word variations have been searched)

#3	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] explode all trees
#4	MeSH descriptor: [Depressive Disorder] this term only and with qualifier(s): [Therapy – TH]
#5	MeSH descriptor: [Depression] this term only and with qualifier(s): [Therapy – TH]
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Transcranial Magnetic Stimulation] explode all trees
#8	(repetiti* or repeat*) near (Transcrani* or Magnet* or Stimul*):ti,ab,kw (Word variations have been searched)
#9	rTMS:ti,ab,kw (Word variations have been searched)
#10	#7 or #8 or #9
#11	#6 and #10 in Cochrane Reviews (Reviews and Protocols), Other Reviews, Methods Studies, Technology Assessments and Economic Evaluations
47 Hits	

PubMed Search String

Search Name: **rTMS for TRD**
Date of Search: 30.12.2016
((Major Depressive Disorder OR Severe Depressive Disorder OR Treatment-Resistant Depressive Disorder OR Major Depression OR Severe Depression OR “Depressive Disorder/therapy”[Majr] OR “Depression/therapy”[Majr])) AND (Transcranial Magnetic Stimulation OR repetitive Transcranial Magnetic Stimulation OR rTMS[tiab]) Filters: Systematic Reviews/Meta-Analyses
Total: 126 Hits

Database: PsycINFO <1806 to January Week 5 2017>

1	exp Major Depression/(110594)
2	((major or severe) adj3 depress*).ti,ab. (41312)
3	exp Treatment Resistant Depression/(1828)
4	1 or 2 or 3 (120952)
5	exp Transcranial Magnetic Stimulation/(6458)
6	((repetiti* or repeat*) adj3 (Transcrani* adj3 Magnet* Stimul*)).ti,ab. (2235)
7	rTMS.ti,ab. (2310)
8	5 or 6 or 7 (6821)
9	4 and 8 (971)
10	limit 9 to (“0830 systematic review” or 1200 meta analysis) (58)
11	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or “research synthesis” or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not “psycinfo database”) or pubmed or scopus or “sociological abstracts” or “web of science”).ab. or (“cochrane database of systematic reviews” or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/or Meta-Analysis.pt. (59199)
12	9 and 11 (121)
13	10 or 12 (122)
08.02.2017	

Search strategy for primary studies

Cochrane database

Search Name: **rTMS for TRD**	
Last Saved: 07/02/2017 15:05:35.760	
ID	Search
#1	MeSH descriptor: [Depression] this term only
#2	MeSH descriptor: [Depressive Disorder] explode all trees
#3	MeSH descriptor: [Depressive Disorder, Major] this term only
#4	MeSH descriptor: [Depressive Disorder, Treatment-Resistant] this term only
#5	depressi* or dysthymic or melancholia or TRD or “involutional psychos*” or paraphrenia:ti,ab,kw
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Transcranial Magnetic Stimulation] this term only
#8	((transcranial or trans-cranial) near (magnetic near stimulation*)) or rtms or tms:ti,ab,kw
#9	#7 or #8
#10	#6 and #9 Online Publication Date from Nov 2014 to Feb 2017 (Word variations have been searched)
#11	#6 and #9 Publication Year from 2014 to 2017
#12	#10 or #11 in Trials
176 Hits	

Embase

No.	Query Results	Results	Date
#14.	‘depression’/mj OR ‘major depression’/mj OR ‘treatment resistant depression’/mj OR depressi*:ti,ab OR dysthymic:ti,ab OR melancholia:ti,ab OR trd:ti,ab OR ‘involutional psychos*’:ti,ab OR paraphrenia:ti,ab AND (‘transcranial magnetic stimulation’/mj OR ((transcranial OR ‘trans cranial’) NEAR/1 (‘magnetic stimulation*’ OR rtms OR tms)):ab,ti) AND [20-2-2014]/sd NOT [6-2-2017]/sd AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) OR (‘depression’/mj OR ‘major depression’/mj OR ‘treatment resistant depression’/mj OR depressi*:ti,ab OR dysthymic:ti,ab OR melancholia:ti,ab OR trd:ti,ab OR ‘involutional psychos*’:ti,ab OR paraphrenia:ti,ab AND (‘transcranial magnetic stimulation’/mj OR ((transcranial OR ‘trans cranial’) NEAR/1 (‘magnetic stimulation*’ OR rtms OR tms)):ab,ti) AND [20-2-2014]/sd NOT [6-2-2017]/sd AND (‘clinical trial’/de OR ‘clinical trial (topic)’/de OR ‘controlled clinical trial’/de OR ‘controlled study’/de OR ‘double blind procedure’/de OR ‘major clinical study’/de OR ‘multicenter study’/de OR ‘randomized controlled trial’/de OR ‘randomized controlled trial (topic)’/de))	351	7 Feb 2017
#13.	‘depression’/mj OR ‘major depression’/mj OR ‘treatment resistant depression’/mj OR depressi*:ti,ab OR dysthymic:ti,ab OR melancholia:ti,ab OR trd:ti,ab OR ‘involutional psychos*’:ti,ab OR paraphrenia:ti,ab AND (‘transcranial magnetic stimulation’/mj OR ((transcranial OR ‘trans cranial’) NEAR/1 (‘magnetic stimulation*’ OR rtms OR tms)):ab,ti) AND [20-2-2014]/sd NOT [6-2-2017]/sd AND (‘clinical trial’/de OR ‘clinical trial (topic)’/de OR ‘controlled clinical trial’/de OR ‘controlled study’/de OR ‘double blind procedure’/de OR ‘major clinical study’/de OR ‘multicenter study’/de OR ‘randomized controlled trial’/de OR ‘randomized controlled trial (topic)’/de)	351	7 Feb 2017

#12.	'depression'/mj OR 'major depression'/mj OR 'treatment resistant depression'/mj OR depressi*:ti,ab OR dysthymic:ti,ab OR melancholia:ti,ab OR trd:ti,ab OR 'involutional psychos*':ti,ab OR paraphrenia:ti,ab AND ('transcranial magnetic stimulation'/mj OR ((transcranial OR 'trans cranial') NEAR/1 ('magnetic stimulation*' OR rtms OR tms)):ab,ti) AND [20-2-2014]/ sd NOT [6-2-2017]/sd	752	7 Feb 2017
#11.	'depression'/mj OR 'major depression'/mj OR 'treatment resistant depression'/mj OR depressi*:ti,ab OR dysthymic:ti,ab OR melancholia:ti,ab OR trd:ti,ab OR 'involutional psychos*':ti,ab OR paraphrenia:ti,ab AND ('transcranial magnetic stimulation'/mj OR ((transcranial OR 'trans cranial') NEAR/1 ('magnetic stimulation*' OR rtms OR tms)):ab,ti) AND [20-2-2014]/ sd NOT [6-2-2017]/sd AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	107	7 Feb 2017
#10.	'depression'/mj OR 'major depression'/mj OR 'treatment resistant depression'/mj OR depressi*:ti,ab OR dysthymic:ti,ab OR melancholia:ti,ab OR trd:ti,ab OR 'involutional psychos*':ti,ab OR paraphrenia:ti,ab AND ('transcranial magnetic stimulation'/mj OR ((transcranial OR 'trans cranial') NEAR/1 ('magnetic stimulation*' OR rtms OR tms)):ab,ti) AND [20-2-2014]/ sd NOT [6-2-2017]/sd	752	7 Feb 2017
#9.	'depression'/mj OR 'major depression'/mj OR 'treatment resistant depression'/mj OR depressi*:ti,ab OR dysthymic:ti,ab OR melancholia:ti,ab OR trd:ti,ab OR 'involutional psychos*':ti,ab OR paraphrenia:ti,ab AND ('transcranial magnetic stimulation'/mj OR ((transcranial OR 'trans cranial') NEAR/1 ('magnetic stimulation*' OR rtms OR tms)):ab,ti)	2,377	7 Feb 2017
#8.	'transcranial magnetic stimulation'/mj OR ((transcranial OR 'trans cranial') NEAR/1 ('magnetic stimulation*' OR rtms OR tms)):ab,ti	15,176	7 Feb 2017
#7.	((transcranial OR 'trans cranial') NEAR/1 ('magnetic stimulation*' OR rtms OR tms)):ab,ti	14,343	7 Feb 2017
#6.	'transcranial magnetic stimulation'/mj	7,453	7 Feb 2017
#5.	'depression'/mj OR 'major depression'/mj OR 'treatment resistant depression'/mj OR depressi*:ti,ab OR dysthymic:ti,ab OR melancholia:ti,ab OR trd:ti,ab OR 'involutional psychos*':ti,ab OR paraphrenia:ti,ab	435,603	7 Feb 2017
#4.	depressi*:ti,ab OR dysthymic:ti,ab OR melancholia:ti,ab OR trd:ti,ab OR 'involutional psychos*':ti,ab OR paraphrenia:ti,ab	409,946	7 Feb 2017
#3.	'treatment resistant depression'/mj	808	7 Feb 2017
#2.	'major depression'/mj	22,274	7 Feb 2017
#1.	'depression'/mj	129,167	7 Feb 2017

Medline via Ovid

Database: Ovid MEDLINE(R) <1946 to January Week 4 2017>, Ovid MEDLINE(R) Epub Ahead of Print <February 06, 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <February 06, 2017>, Ovid MEDLINE(R) Daily Update <February 06, 2017>, Ovid MEDLINE(R) Versions	
1	Depression/(93575)
2	exp Depressive Disorder/(94576)
3	Depressive Disorder, Major/(24010)
4	Depressive Disorder, Treatment-Resistant/(667)
5	(depressi* or dysthymic or melancholia or TRD or "involutional psychos*" or paraphrenia).ti,ab. (311657)
6	1 or 2 or 3 or 4 or 5 (355014)
7	Transcranial Magnetic Stimulation/(8595)
8	(((transcranial or trans-cranial) adj2 (magnetic adj2 stimulation*)) or rtms or tms).mp. (16992)

9	7 or 8 (16992)
10	6 and 9 (1898)
11	remove duplicates from 10 (1861)
12	limit 11 to ed=20141120-20170206 (312)
13	limit 12 to (clinical study or clinical trial, all or comparative study or controlled clinical trial or pragmatic clinical trial or randomized controlled trial) (62)
14	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/not humans.sh.) (3444658)
15	12 and 14 (129)
16	13 or 15 (134)
07.02.2017	

Database: PsycINFO <1806 to January Week 5 2017>

1	exp Major Depression/(110594)
2	(depressi* or dysthymic or melancholia or TRD or “involutional psychos*” or paraphrenia).ti,ab. (238680)
3	1 or 2 (245404)
4	exp Transcranial Magnetic Stimulation/(6458)
5	(((transcranial or trans-cranial) adj2 (magnetic adj2 stimulation*)) or rtms or tms).mp. (8579)
6	4 or 5 (8579)
7	3 and 6 (1496)
8	limit 7 to (“0300 clinical trial” or “0451 prospective study” or “0453 retrospective study”) (130)
9	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.sh. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/not humans.sh.) (598811)
10	7 and 9 (636)
11	8 or 10 (662)
12	limit 11 to yr=”2014-2017” (188)
07.02.2017	

DESCRIPTION OF THE EVIDENCE USED

Guidelines for diagnosis and management

Table A 1: Overview of guidelines: diagnosis and management of MDD

Society/organisation issuing guidance	Date of issue	Quality appraisal (AGREE II)	Methodology (evidence and recommendations)	Summary of recommendation	Level of evidence
American Psychiatric Association (APA) [20]	2000, partial update 2005, revision 2010	Scope and purpose: 0,64 Stakeholder involvement: 0,31 Rigour of development: 0,45 Clarity of presentation: 0,61 Applicability: 0,25 Editorial Independencde: 0,88 Global quality of the CPG E1: 4 E2: 4	Each recommendation falls into one of three categories of endorsement: [I] Recommended with substantial clinical confidence [II] Recommended with moderate clinical confidence [III] May be recommended on the basis of individual circumstances	For patients whose symptoms have not responded adequately to medication, ECT remains the most effective form of therapy and should be considered. In patients capable of adhering to dietary and medication restrictions, an additional option is changing to a nonselective MAOI after allowing sufficient time between medications to avoid deleterious interactions. Transdermal selegiline, a relatively selective MAO B inhibitor with fewer dietary and medication restrictions, or transcranial magnetic stimulation could also be considered. Vagus nerve stimulation (VNS) may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT.	I Changing to MAOI: II Leaving sufficient time between medications: I II III
World Federation of Societies of Biological Psychiatry (WFSBP) [23]	2013 (update or previous guideline	Scope and purpose: 0,69 Stakeholder involvement: 0,42 Rigour of development: 0,51 Clarity of presentation: 0,64 Applicability: 0,06 Editorial Independence: 0,58 Global quality of the CPG: E1: 5 E2: 4	***Evidence-based classification of recommendations*** *Strength of evidence for its efficacy, safety, and feasibility:* *CE A:* Full evidence from controlled trials *CE B:* Limited positive evidence from controlled trials *CE C:* Evidence from uncontrolled studies or case reports/expert opinion *CE D:* Inconsistent results *CE E*: Negative evidence *CE F*: Lack of evidence.	There is currently insufficient evidence for the clinical efficacy that allows recommending TMS in the standard clinical setting. Further research is needed.	(CE D, RG 5)

Society/organisation issuing guidance	Date of issue	Quality appraisal (AGREE II)	Methodology (evidence and recommendations)	Summary of recommendation	Level of evidence
			Recommendations derived from CE and additional aspects (safety, tolerability, and interaction potential) RG 1: CE A evidence and good risk – benefit ratio RG 2: CE A evidence and moderate risk – benefit ratio RG 3: CE B evidence RG 4: CE C evidence RG 5: CE D evidence		
Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPPN) [21]	2015	Scope and purpose: 0,69 Stakeholder involvement: 0,62 Rigour of development: 0,51 Clarity of presentation: 0,64 Applicability: 0,26 Editorial Independence: 0,78	*Evidence level:* Ia: evidence from meta-analysis of minimum 3 RCTs Ib: evidence from minimum 1 RCT or 1 meta-analysis of less than 3 RCTs IIa: evidence from at least a good quality non-RCT IIb: evidence from a quasi-experimental, good quality descriptive study III: evidence from a good non-experimental observational study IV: evidence from expert committees, standpoints, clinical experience *Recommendations:* A: "must be done": evidence level Ia or Ib B: "should be done": evidence level II or III or extrapolated Ia or Ib 0:"Can be done": evidence level IV or extrapolation of IIa, IIb or III. There were no clinical studies of good quality available.	HF-rTMS can be applied in treatment-resistant patients who have previously failed one antidepressant trial.	0
Spanish Ministry of Health (AVALIA-t) [73]	2014	Scope and purpose: 0,83 Stakeholder involvement: 0,83 Rigour of development: 0,79 Clarity of presentation: 0,72 Applicability: 0,71	SIGN methodology is applied. For qualitative evidence (Q): evidence obtained from relevant and good quality qualitative studies. This category is not considered by SIGN methodology.	TMS as an add on therapy for treatment resistant depression Currently, transcranial magnetic stimulation is not recommended for the treatment of depression due to the uncertainty related to its clinical efficacy.	B

Society/organisation issuing guidance	Date of issue	Quality appraisal (AGREE II)	Methodology (evidence and recommendations)	Summary of recommendation	Level of evidence
		Editorial Independence: 0,67 Global quality of the CPG: E1: 6 E2:		Electroconvulsive therapy should be considered as an alternative treatment in patients with severe depression, mainly if there is a need of a rapid response due to a high number of suicidal thoughts, severe physical deterioration, or when other treatments have failed. The decision of using ECT should be taken with the patient/or his/her family, taking into account the diagnosis, type and severity of symptoms, clinical history, balance between risk and benefits, other alternatives, and patients preferences. If ECT is necessary, it is recommended to put a special emphasis on offering all the necessary information, focusing on the procedure`s purpose, secondary effects, and treatment plan.	A Q Q

Abbreviations: APA American Psychiatric Association, AGREE II Advancing guideline development, reporting and evaluation in healthcare, CPG clinical practice guideline, DGPPPN Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde, ECT electroconvulsive therapy, HF-rTMS high-frequency repetitive transcranial magnetic stimulation, MAOI monoamine oxidase inhibitors, MAOB monoamine oxidase B, RCT randomized controlled trial, SIGN Scottish Intercollegiate Guidelines Network

Table A2: Overview of guidelines focusing on rTMS

Society/organisation issuing guidance	Date of issue	Quality appraisal (AGREE II)	Methodology (evidence and recommendations)	Summary of recommendation	Level of evidence
Canadian Network for Mood and Anxiety Treatments (CANMAT) [11]	2009 (updated in 2016)	Scope and purpose: 0,61 Stakeholder involvement: 0,44 Rigour of development: 0,46 Clarity of presentation: 0,64 Applicability: 0,13 Editorial Independence: 0,50 Global quality of the CPG: E1: 5 E2: 4	CANMAT-defined criteria for level of evidence. Recommendations for lines of treatment are based on the quality of evidence and clinical expert consensus.	rTMS is considered first line treatment for patients who have failed at least 1 antidepressant. Both HF to the left DLPFC and LF to the right DLPFC are first-line rTMS protocol recommendations. A second-line recommendation is to switch non-responders to the other stimulation protocol. Bilateral stimulation is considered a second line rTMS protocol. Stimulation to bilateral DLPFC is recommended as a third-line rTMS protocol. TBS protocols are recommended as second-line.	Acute efficacy: level 1; maintenance efficacy: level 3, safety and tolerability: level 1 Level 1 Level 3 Level 1 Level 3 Level 3

Society/organisation issuing guidance	Date of issue	Quality appraisal (AGREE II)	Methodology (evidence and recommendations)	Summary of recommendation	Level of evidence
National Institute for Health and Clinical Excellence (NICE) [22]	2015	Scope and purpose: 0,61 Stakeholder involvement: 0,67 Rigour of development: 0,65 Clarity of presentation: 0,72 Applicability: 0,71 Editorial Independence: 0,67 Global quality of the CPG: E1: 5 E2: 5	*Standard arrangements* The evidence should be valid, relevant and of good quality, sufficiently consistent in nature. It should show that the frequency and severity of adverse effects of the procedure are similar to, or less than, those of any comparable and established procedures and should show benefits within an appropriate time of the procedure. *Special arrangements* A special arrangements recommendation states that clinicians using the procedure must inform the clinical governance lead in their trust, tell the patient about the uncertainties regarding the safety and efficacy of the procedure and collect further data by means of audit or research. The Committee recommends these arrangements because there are significant uncertainties in the evidence on efficacy or safety, or an inadequate quantity of evidence. The Committee may also consider the balance of risks and benefits of the procedure to see if special arrangements should be in place. This recommendation is often made when the procedure is considered to be an emerging practice in the NHS. *Do not use* When the evidence suggests that a procedure has no efficacy or poses unacceptable safety risks.	The evidence on rTMS for depression shows no major safety concerns. The evidence on its efficacy in the short-term is adequate, although the clinical response is variable. rTMS for depression may be used with normal arrangements for clinical governance and audit. During the consent process, clinicians should, in particular, inform patients about the other treatment options available, and make sure that patients understand that the procedure may not bring them benefit. NICE encourages publication of further evidence on patient selection, details of the precise type and regime of stimulation used, the use of maintenance treatment and long-term outcomes.	Standard arrangement
Royal Australian and New Zealand College of Psychiatrists CPG for mood disorders (RANZCP)	2015	Scope and purpose: 0,61 Stakeholder involvement: 0,44 Rigour of development: 0,46 Clarity of presentation: 0,64 Applicability: 0,13 Editorial Independence: 0,50 Global quality of the CPG: E1: 5 E2: 4	*Two types of recommendations:* 1, Evidence-based recommendations (EBRs) are formulated when there is a sufficiently consistent evidence from interventional studies to support a recommendation on a given topic. For each EBR, strength of evidence is rated using the NHMRC levels of evidence for interventional studies and is graded accordingly (e.g., EBR I, II, III, or IV). 2, The absence of evidence is not evidence of absence, so a second type of recommendation is also employed and termed a consensus based recommendation (CBR).	rTMS is a safe and effective treatment for more severe presentations of depression and should be considered first-line for psychotic depression or when an immediate response is necessary. Patients with non-psychotic depression may be treated with rTMS once they have failed one or more trials of standard antidepressant medications and psychological therapies.	EBR I EBR I

Society/organisation issuing guidance	Date of issue	Quality appraisal (AGREE II)	Methodology (evidence and recommendations)	Summary of recommendation	Level of evidence
French guideline (Lefaucheur) [74]	2011	Scope and purpose: 0,50 Stakeholder involvement: 0,44 Rigour of development: 0,38 Clarity of presentation: 0,53 Applicability: 0,06 Editorial Independence: 0,33 Global quality of the CPG: E1: 3 E2: 3	Classification (I–IV) of studies according to level of evidence. A Class I study is a prospective, randomized, placebo-controlled clinical trial with blinded outcome assessment in a number of patients that is representative (n ≥25 receiving active treatment). A Class II study is a randomized, placebo-controlled trial with a smaller sample size (n < 25), or a placebo controlled large retrospective study. Class III studies include all other controlled trials with some bias or methodological problems. Class IV studies are uncontrolled studies, case series, and case reports. These classifications are applied to rate the level of evidence (A–C). Level A (''definitely effective or ineffective''): at least 2 Class I studies or one Class I study and at least 2 consistent, Class II studies. Level B (''probably effective or ineffective''): at least 2 Class II studies or one Class II study and at least 2 consistent, Class III studies. Level C (''possibly effective or ineffective''): one Class II study or at least 2 Class III studies are required. No recommendation will be made in the absence of at least 2 Class III studies providing similar results on the same type of clinical features with similar stimulation methods.	Definite antidepressant effect of high frequency rTMS on the left DLPFC for the treatment of MDD. There is probably no difference in the effect between right and left side stimulations. No recommendation for bilateral rTMS combining HF rTMS of the left DLPFC and LF rTMS of the right DLPFC.	Level A Level C Level B
Rossi 2009 [7]	2009	Scope and purpose: 0,44 Stakeholder involvement: 0,39 Rigour of development: 0,09 Clarity of presentation: 0,19 Applicability: 0,06 Editorial Independence: 0,04 Global quality of the CPG: E1: 3 E2: 2	Consensus	No recommendations. Information about safety, ethical considerations, and application of the technology. The present updated guideline discusses safety of conventional TMS protocols, addresses the undesired effects and risks of emerging TMS interventions, the applications of TMS in patients with implanted electrodes in the central nervous system, and safety aspects of TMS in neuroimaging environments. It covers recommended limits of stimulation parameters and other important precautions, monitoring of subjects, expertise of the rTMS team, and ethical issues. While all the recommendations are expert based, they utilize published data to the extent possible.	

Society/organisation issuing guidance	Date of issue	Quality appraisal (AGREE II)	Methodology (evidence and recommendations)	Summary of recommendation	Level of evidence
Clinical neurophysiology [5]	2015	Scope and purpose: 0,61 Stakeholder involvement: 0,36 Rigour of development: 0,31 Clarity of presentation: 0,50 Applicability: 0,06 Editorial Independence: 0,25 Global quality of the CPG: E1: 3 E2: 3	Critical assessment of all selected publications in order to classify them according to the criteria used in the previos French version of the guideline (Lefaucheur et al., 2011a) and derived from those proposed by the European Federation of Neurological Societies (Brainin et al., 2004).	Definite antidepressant effect of HF rTMS of the left DLPFC. Probable antidepressant effect of LF rTMS of the right DLPFC and probably no differential antidepressant effect between right LF rTMS and left HF rTMS. No recommendation for bilateral rTMS combining HF rTMS of the left DLPFC and LF rTMS of the right DLPFC. Definite antidepressant effect of rTMS of DLPFC in unipolar depression, but no recommendation for bipolar depression. Antidepressant effect of rTMS of DLPFC is probably additive to the efficacy of antidepressant drugs and possibly potentiating. No recommendation for the overall respective antidepressant efficacy of rTMS of DLPFC compared to ECT.	Level A Level B Level B Level A Level B Level C

Abbreviations: AGREE II Advancing guideline development, reporting and evaluation in healthcare, CANMAT Canadian Network for Mood and Anxiety Treatments, CBR consensus based recommendation, CPG clinical practice guideline, DLPFC dorsolateral prefrontal cortex, EBR evidence-based recommendations, ECT electroconvulsive therapy, HF-rTMS high-frequency repetitive transcranial magnetic stimulation, LF low frequency, MDD major depressive disorder, NHMRC National Health and Medical Research Council, NICE National Institute for Health and Clinical Excellence, NHS National Health Service, RANZCP Royal Australian and New Zealand College of Psychiatrists

Main characteristics of systematic reviews assessed for eligibility

Table A 3: Systematic reviews comparing rTMS with sham rTMS

Author and year	Study type	Number of patients, number of RCTs	Aim of the study	Intervention(s) vs Comparison(s)	Main endpoints	Inclusion criteria	Included studies	Period searched	AMSTAR Score (# no, can't answer, not applicable)
Berlim, 2014 [75]	SR	1371 pts, 29 RCTs	To summarize the evidence on HF rTMS for treating MDD, including: (a) response and remission; (b) utility of HF rTMS as mono- or add-on therapy; (c) differential efficacy of HF rTMS in unipolar vs in mixed samples, and in pts with TRD vs in pts with a less resistant illness; (d) impact of the strategy for managing missing data and of alternative stimulation parameters on the efficacy of HF rTMS; (e) its acceptability (indexed by drop-out rates).	HF rTMS vs sham rTMS	Response, remission	*Inclusion:* sham controlled double-blind RCTs with parallel or crossover design, pts with MDD (diagnosed according to DSM-IV or ICD -10), age 18-75 yrs, HF rTMS to the left DLPFC for ≥10 sessions, English language	Avery 2006, Anderson 2007, Bakim 2012, Berman 2000, Blumberger 2012, Boutros 2002, Fitzgerald 2003, Fitzgerald 2012, Garcia-Toro 2001, George 1997, George 2000, George 2010, Hernandez-Ribas 2013, Holtzheimer 2004, Hoppner 2003, Koerselman 2004, Loo 2007, Mogg 2008, Mosimann 2004, Nahas 2003, O'Reardon 2007, Padberg 2002, Palliere-Martinot 2010, Rossini 2005, Stern 2007, Su 2005,Triggs 2010, Zhang 2011, Zheng 2010	1995-2012	10 (#2 can't answer)
Berlim, 2013 [76]	SR and MA	392 pts, 6 RCTs	To examine whether HF rTMS can hasten the therapeutic effects of standard antidepressants in MDD.	HF rTMS vs sham rTMS (all the patients concomitant new anti-depressant medication)	Response, remission, acceptability	*Inclusion:* sham controlled double-blind RCTs with parallel or crossover design, ≥ 5 pts per study arm, pts with unipolar or bipolar MDD, age 18-75 yrs, HF rTMS to the left DLPFC for ≥ 5 sessions, started concomitantly with new antidepressant medication, English language	Bretlau 2008, Garcia-Toro 2001, Herwig 2007, Huang 2012, Rossini 2005, Rumi 2005	1995-2012	10 (#2 can't answer)

Author and year	Study type	Number of patients, number of RCTs	Aim of the study	Intervention(s) vs Comparison(s)	Main endpoints	Inclusion criteria	Included studies	Period searched	AMSTAR Score (# no, can't answer, not applicable)
Brunoni, 2016 [77]	SR and NMA	4233 pts, 81 RCTs	To establish a clinically meaningful hierarchy of efficacy and tolerability of different rTMs modalities for MDD.	rTMS (HF, LF, B, pTMS, aTMS, sTMS, DTMS, TBS) vs sham rTMS	Response, remission	*Inclusion:* RCTs, pts with unipolar or bipolar depression	N/A	n.a.-2016	7 (#4,5,6,11 no)
Gaynes, 2014 [78]	SR	782 pts, 18 RCTs	To evaluate the efficacy of rTMS in pts with TRD (2 or more antidepressant failures).	rTMS vs sham rTMS	Standardized mean difference in depression scores, response, remission	*Inclusion:* RCTs, good or fair quality meta-analyses, any duration, pts with MDD that failed to achieve improvement after 2 or more adequate antidepressant medication treatments	Avery 2006, Bakim 2012, Blumberger 2012, Bocchio-Chiavetto 2008, Boutros 2002, Fitzgerald 2003, Fitzgerald 2006, Fitzgerald 2012, Garcia-Toro 2001, Garcia-Toro 2006, Holtzheimer 2004, Kauffmann 2004, Padberg 1999, Pallanti 2010, Pascual-Leone 1996, Su 2005, Triggs 2010, Zheng 2010	1980-2013	10 (#5 no)
Hovington, 2013 [79]	SR of SRs	11 SRs	To summarize several MAs exploring the efficacy of rTMS in either MDD or schizophrenia in order to examine the methodologies that increase the efficacy of rTMS.	rTMS vs sham rTMS	Standardized mean difference in depression scores, response, remission	*Inclusion:* age ≥ 18 yrs, primary diagnosis of MDD, English language, published in peer-reviewed journal, MA provides effect sizes of primary studies	Burt 2002, Couturier 2005, Gross 2007, Herrmann 2006, Holtzheimer 2001, Kozel 2002, Lam 2008, Martin 2003, McNamara 2001, Schutter 2009, Slotema 2010	1993-2010	4 (#2 can't answer, #3-5,7,8,10 no)
HQO, 2016 [13]	SR	rTMS vs sham rTMS: 1156 pts, 23 RCTs	To examine the antidepressant efficacy of rTMS in patients with TRD.	HF rTMS vs sham rTMS, HF rTMS vs ECT	Standardized mean difference in depression scores, response, remission	*Inclusion:* RCTs, age ≥ 18 yrs, HF rTMS for ≥ 10 sessions, only unipolar pts or max. 20% bipolar pts, ≥ 80% of pts with TRD	Avery 1999, Avery 2006, Bakim 2012, Berman 2000, Blumberger 2012, Bretlau 2008, Boutros 2002, Chen 2013, Fitzgerald 2003, Fitzgerald 2012, Garcia-Toro 2001, George 2010, Holtzheimer 2004, Hoppner 2003, Loo 1999, Loo 2007, Mogg 2008, Mosimann 2004, O'Reardon 2007, Padberg 2002, Stern 2007, Su 2005, Triggs 2010	1994-2014	9 (#4,5 no)
Kedzior, 2014a [80]	SR and MA	801 pts, 18 RCTs	To update a previous SR of the authors (Kedzior 2014b), to compare the overall mean	rTMS (L, R, B) vs sham rTMS (L, R, B)	Standardized mean difference in	I*nclusion:* sham controlled RCTs	Aguirre 2011, Bakim 2012, Blumberger 2012, Chen 2013, Fitzgerald 2012, George 2010,	2008-2013	9 (#4,5 no)

Author and year	Study type	Number of patients, number of RCTs	Aim of the study	Intervention(s) vs Comparison(s)	Main endpoints	Inclusion criteria	Included studies	Period searched	AMSTAR Score (# no, can't answer, not applicable)
			weighted effect sizes of the studies in the previous SR with the new studies, and to find out if any patient characteristics or TMS parameters would be associated with the short-term antidepressant properties of rTMS.		depression scores	with parallel design, HAMD, BDI or MADRS scales, pts with MDD (diagnosed according to DSM-IV or ICD-10)	He 2011, Hernandez-Ribas 2013, Huang 2012, Lingeswaran 2011, Pallanti 2010, Palliere-Martinot 2010, Peng 2012, Ray 2011, Spampinato 2013, Speer 2013, Triggs 2010, Zheng 2010		
Kedzior, 2014b [81]	SR and MA	1583 pts, 40 RCTs,	To apply a uniform and transparent meta-analytical procedure to reanalyse the data from the past 13 MA in order to find out if the new MA would produce only a moderate short-term antidepressant effect or it would increase due to the uniform statistical approach, and to test if the inclusion of more data than any one of the past MA alone would allow to detect significant predictors of the short-term response to rTMS due to a higher statistical power of an overall analysis.	rTMS (L, R, B) vs sham rTMS (L, R, B)	Standardized mean difference in depression scores	*Inclusion:* double-blind RCTs with parallel design, pts with MDD (diagnosed according to DSM-IV or ICD -10), HAMD, BDI or MADRS scales, adequate data to compute effect sizes, depression measured at baseline and last session of rTMS or sham	Anderson 2007, Avery 1999, Avery 2006, Berman 2000, Bretlau 2008, Bortolomasi 2007, Boutros 2002, Buchholtz 2004, Eschweiler 2000, Fitzgerald 2003, Fitzgerald 2006, Garcia-Toro 2001a, Garcia-Toro 2001b, Garcia-Toro 2006, George 1997, George 2000, Hausmann 2004, Herwig 2007, Höppner 2003, Holtzheimer 2004, Januel 2006, Kauffmann 2004, Kimbrell 1999, Klein 1999, Koerselman 2004, Loo 1999, Loo 2007, Loo 2003, Manes 2001, Mogg 2008, Mosimann 2004, Nahas 2003, O'Reardon 2007, Padberg 2002, Padberg 1999, Poulet 2004, Rossini 2005, Rumi 2005, Stern 2007, Su 2005	1997-2008	8 (#5 no, #3,4 not applicable)
Kedzior, 2015 [82]	SR and MA	495 pts, 16 RCTs	To investigate the durability of the antidepressant effect of rTMS compared to sham using a continuous outcome instead of response rates.	HF rTMS vs. sham rTMS	Standardized mean difference in depression scores	*Inclusion:* double-blind RCTs with parallel design, pts with MDD (diagnosed according to DSM-IV or ICD -10), HAMD or MADRS scales, HF rTMS to the left DLPFC	Avery 1999, Anderson 2007, Bretlau 2008, Bortolomasi 2007, Buchholtz 2004, Eschweiler 2000, Garcia-Toro 2001a, Garcia-Toro 2001b, Holtzheimer 2004, Koerselman 2004, Manes 2001, Mogg 2008, Huang 2012, Poulet 2004, Rossini 2005, Triggs 2010	n.a.–2013	10 (#4 no)
Lepping, 2014 [83]	SR	rTMS vs sham rTMS:	To assess the clinical relevance of the efficacy of rTMS.	rTMS (HF, LF, B) vs sham rTMS,	Standardized mean difference in	*Inclusion:* human subjects with depression irrespective of the	Avery 2006, Bakim 2012, Bretlau 2008, Chen 2013, Garcia-Toro 2001, Garcia-Toro 2006, George	n.a.-2014	5 (no or not clear #4,5,7,8,9,10)

Author and year	Study type	Number of patients, number of RCTs	Aim of the study	Intervention(s) vs Comparison(s)	Main endpoints	Inclusion criteria	Included studies	Period searched	AMSTAR Score (# no, can't answer, not applicable)
		1646 pts, 32 RCTs		rTMs vs ECT	depression scores	subtype and criteria used, rTMS as mono- or add-on therapy, HAMD scale, RCTs or non-RCTs, published in peer-reviewed journal, full-text available, sample size for each study arm reported	2010, George 1997, George 2000, Hansen 2004, Hausmann 2004, Hernandez-Ribas 2013, Herwig 2003, Herwig 2007, Holtzheimer 2004, Januel 2006, Kauffmann 2004, Klein 1999, Koerselman 2004, Loo 2006, Manes 2001, Martinot 2010, Moller 2006, Mosimann 2004, Nahas 2001, O'Reardon 2007, Padberg 2002, Rossini 2005, Stern 2007, Su 2005, Triggs 2010, Zheng 2010		
Liu, 2014 [84]	SR and MA	279 pts, 7 RCTs	To evalute the efficacy and tolerability of rTMS used as an augmentative therapy.	rTMS vs sham rTMS (all the patients with stable andidepressant treatment)	Response, remission	*Inclusion:* double-blind, sham controlled RCTs, rTMS as augmentation, age 18-75 yrs, pts with MDD, psychotic symptoms excluded, HAMD, MADRS scales, English language	Bakim 2012, Bretlau 2008, Chen 2013, Garcia-Toro 2001, Garcia-Toro 2006, Martinot 2010, Rossini 2005	1995-2013	9 (#2 and 5 no)
Leggett, 2015 [85]	SR and MA	rTMS vs sham rTMS: 1903 pts, 45 RCTs	To establish the efficacy and optimal protocol for rTMS among adults and youth with TRD.	rTMS vs sham rTMS, rTMS vs ECT, HF rTMS vs LF rTMS, B-rTMS vs unilateral rTMS	Response, remission	*Inclusion:* TRD or pts who have had $\geq$ 2 previous treatments, age >18 yrs, bipolar or unipolar depression, HAMD, MADRS, BDI scales, not been treated with rTMS prior to the study, RCT	Avery 2006, Bakim 2012, Bares 2009, Berman 2000, Blumberger 2012, Boutros 2002, Chen 2013, Fitzgerald 2003, Fitzgerald 2012, Garcia-Toro 2006, George 2010, Hernandez-Ribas 2013, Holtzheimer 2004, Jorge 2004, Jorge 2008, Kauffmann 2004, Loo 2007, Manes 2001, Mantovani 2013, McDonald 2006, Mosimann 2004, O'Reardon 2007, Padberg 2002, Palliere-Martinot 2010, Peng 2012, Rossini 2005, Stern 2007, Su 2005, Zheng 2010	n.a.–2014	9 (#4,5 no)

Author and year	Study type	Number of patients, number of RCTs	Aim of the study	Intervention(s) vs Comparison(s)	Main endpoints	Inclusion criteria	Included studies	Period searched	AMSTAR Score (# no, can't answer, not applicable)
Leggett, 2014 [86]	SR and MA	rTMS vs sham rTMS: 1903 pts, 45 RCTs	To summarize the available evidence on rTMS for pts with TRD.	rTMS vs sham rTMS, rTMS vs ECT, HF rTMS vs LF rTMS, B-rTMS vs unilateral rTMS, rTMS vs various other rTMS protocols	Standardized mean difference in depression scores, response, remission	Pts with TRD, age ≥ 18 yrs, bipolar or unipolar depression, HAMD, MADRS or BDI scales, not treated with rTMS before, RCT, reporting on efficacy in comparison to sham, pharmacological therapy, ECT or cognitive therapy or one type of rTMS vs another type of rTMS	Avery 1999, Avery 2006, Baeken 2013, Bakim 2012, Bares 2009, Berman 2000, Blumberger 2012, Bretlau 2008, Bortolomasi 2007, Boutros 2002, Chen 2013, Fitzgerald 2003, Fitzgerald 2006, Fitzgerald 2012, Garcia-Toro 2001, Garcia-Toro 2006, George 2010, Hernandez-Ribas 2013, Holtzheimer 2004, Jorge 2004, Jorge 2008, Kauffmann 2004, Lisanby 2009, Loo 1999, Loo 2007, Loo 2003, Manes 2001, Mantovani 2013, McDonald 2006, Moller 2006, Moser 2002, Mosimann 2004, O'Reardon 2007, Padberg 2002, Padberg 1999, Palliere-Martinot 2010, Pascal-Leone 1996, Peng 2012, Rossini 2005, Speer 2009, Speer 2013, Stern 2007, Su 2005, Triggs 2010, Zheng 2010	n.a.–2014	9 (#4,5 no)
Serafini, 2014 [87]	SR	rTMS vs sham rTMS: 265 pts, 5 RCTs	Systematically investigate the role of rTMS in improving neurocognition in patients with TRD	L-rTMS vs sham rTMS, L-rTMs vs ECT, DTMS, rTMS of the anterior middle frontal gyrus vs sham rTMS, R-rTMS, L-rTMS	Depression severity, verbal memory and fluency, response and remission, working memory, attention, visuospatial memory	Inclusion: published in peer-reviewed journal, pts with TRD, analysis of the effect of neurocognitive functioning	Avery 2006, Fitzgerald 2009, Hoy 2012, Padberg 1999, Vanderhasselt 2009	1995-2014	4 (#4,5,7,8,9,10,11 no)

Abbreviations: AMSTAR A MeaSurement Tool to Assess systematic Reviews, aTMS accelerated repetitive transcranial magnetic stimulation, B bilateral, BDI Beck Depression Inventory, B-rTMS bilateral repetitive transcranial magnetic stimulation, DLPFC dorsolateral prefrontal cortex, DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, DTMS deep transcranial magnetic stimulation, ECT electroconvulsive therapy, HAMD Hamilton Depression Scale, HF high frequency, Hz Hertz, ICD International Statistical Classification of Diseases and Related Health Problems, LF low frequency, L-rTMS left-side repetitive transcranial magnetic stimulation, MA meta-analysis, MADRS Montgomery–Åsberg Depression Rating Scale, MDD major depressive disorder, pts patients, N/A not available, pTMS paired transcranial magnetic stimulation, rTMS repetitive transcranial magnetic stimulation, R-rTMS right-side repetitive transcranial magnetic stimulation, RCT randomized controlled trial, sTMS synchronized transcranial magnetic stimulation, SR systematic review, TBS Theta Burst Stimulation, TRD treatment-resistant depression, yrs years

Table A 4 Systematic reviews comparing rTMS with ECT

Author and year	Study type	Number of patients, number of RCTs	Aim of the study	Intervention(s) vs Comparison(s)	Main endpoints	Inclusion criteria	Included studies	Period searched	AMSTAR Score (# no, can't answer, not applicable)
Berlim, 2013 [88]	SR and MA	294 pts, 7 RCTs	To summarize the best available evidence on the comparative efficacy and acceptability of HF-rTMS and ECT for treating MDD.	HF rTMS vs ECT	Standardized mean difference in depression scores, remission, acceptability	*Inclusion:* RCTs with parallel or crossover design, ≥ 5 pts with MDD per study arm, age 18-75 yrs, unipolar or bipolar depression, HF rTMS (≥ 5 Hz) of the left DLPFC vs ECT (bilateral or unilateral) for ≥ 10 and 6 sessions respectively, either as mono-or add-on therapy	Eranti 2007, Grunhaus 2000, Grunhaus 2003, Janicak 2002, Keshtkar 2011, Pidmore 2000, Rosa 2006	1995-2012	9 (#2 can't answer, #4 no)
Micallef-Trigona, 2014 [89]	SR and MA	384 pts, 9 RCTs	To compare ECT with rTMS for the management of TRD. The null hypothesis is being tested: there is no statistically significant difference in the antidepressant efficacy between the two types of treatment.	rTMS vs ECT	Standardized mean difference in depression scores	*Inclusion:* prospective RCTs with parallel design that compare ECT with rTMS, English language, human subjects aged >18 yrs with informed consent, HAMD scale and report on score before and after the treatment, unipolar depression or bipolar with a current depressive episode	Eranti 2007, Grunhaus 2000, Grunhaus 2003, Hansen 2011, Janicak 2002, Keshtkar 2011, O'Connor 2003, Rosa 2006, Schulze-Rauschenbach 2005	1806-2013	6 (#2, #9 can't answer and #4,#5,#7 no)
Vallejo-Torres, 2015 [90]	Eco-nomic eval-uation	n.a. pts, 7 RCTs	To develop a decision analytical model of the cost-effectiveness of ECT vs rTMS for TRD.	rTMS vs ECT	Response, relapse, remission, adverse effect	*Inclusion:* RCTs comparing rTMS with ECT, age 18-75 yrs, unipolar or bipolar MDD starting treatment with ECT or rTMS without new antidepressant therapy, resistance to standard treatment or refractoriness of depression	Dannon 2002, Eranti 2007, Grunhaus 2003, Grunhaus 2000, Janicak 2002, Keshtkar 2011, Rosa 2006	n.a.	Not applicable
Xie, 2013 [91]	SR and MA	395 pts, 9 RCTs	To assess how rTMS stimulus parameters influence the efficacy of rTMS relative to ECT in treating MDD.	rTMS vs ECT	Remission, response, drop-out	*Inclusion:* RCTs comparing rTMS with ECT, HAMD scale, pts >18 yrs without metallic implants or foreign bodies, dementia, personal or family history of epileptic seizures, severe suicidal risk, organic brain damage, severe agitation or delirium, substance abuse, alcohol or drug dependence, and/or medically unfit for general anesthesia, providing informed consent	Eranti 2007, Grunhaus 2000, Grunhaus 2003, Hansen 2011, Janicak 2002, Keshtkar 2011, Pridmore 2000, Rosa 2006, Wang 2004	n.a.-2012	10 (#5 no)

Author and year	Study type	Number of patients, number of RCTs	Aim of the study	Intervention(s) vs Comparison(s)	Main endpoints	Inclusion criteria	Included studies	Period searched	AMSTAR Score (# no, can't answer, not applicable)
Chen, 2017 [92]	SR and MA	L-rTMS vs ECT: 343 pts, 8 RCTs	To assess the efficacy and acceptability of ECT, B-rTMS, R-rTMS, and L-rTMS on MDD.	L-rTMS vs B-rTMS, L-rTMS vs ECT, L-rTMS vs R-rTMS, R-rTMS vs ECT, R-rTMS vs B-rTMS	Response, drop-out	*Inclusion:* RCT, HAMD MADRS or CGI scale, age >18 yrs, pts without metallic implants or foreign bodies, dementia, personal or family history of epileptic seizures, severe suicidal risk, organic brain damage, severe agitation or delirium, substance abuse, alcohol or drug dependence, and/or medically unfit for general anesthesia. Pregnant pts also excluded.	Eranti 2007, Grunhaus 2000, Pridmore 2000, Rosa 2006, Wan 2011, Wang 2004	n.a.-2016	10 (#5 no)
Ren, 2014 [93]	SR and MA	429 pts, 10 RCTs	To compare rTMS and ECT taking into account clinically meaningful out-comes and to investigate the differences in self-rated mood improvement, general mental state, cognitive function and adverse effects.	rTMS vs ECT	Response, remission, acceptability	*Inclusion:* RCTs that compare rTMS with ECT Pts with unipolar or bipolar MDD with or without psychotic features HF of the left DLPFC or LF to the right DLPFC as add-on- or monotherapy ECT at any intensity and localization as add-on- or monotherapy	Dannon 2002, Eranti 2007, Grunhaus 2000, Grunhaus 2003, Hansen 2011, Janicak 2002, Keshtkar 2011, Pridmore 2000, Rosa 2006, Wang 2004	n.a.-2013	10 (#5 no)
HQO, 2016 [13]	SR and MA	HF rTMS vs ECT: 266 pts, 6 RCTs	To examine the antidepressant efficacy of rTMS in patients with TRD.	HF rTMS vs sham rTMS, HF rTMS vs ECT	Standardized mean difference in depression scores, response, remission	*Inclusion:* RCTs, age ≥ 18 yrs, HF rTMS for ≥ 10 sessions, only unipolar pts or max. 20% bipolar pts, ≥ 80% of pts with TRD	Eranti 2007, Grunhaus 2000, Grunhaus 2003, Keshtkar 2011, Pridmore 2000 and Dannon 2002, Rosa 2006	1994-2014	9 (#4,5 no)
Leggett, 2014 [86]	SR and MA	rTMS vs ECT: 205 pts, 6 RCTs	To summarize the available evidence on rTMS for pts with TRD.	rTMS vs sham rTMS, rTMS vs ECT, HF rTMS vs LF rTMS, B-rTMS vs unilateral rTMS, rTMS vs various other rTMS protocols	Standardized mean difference in depression scores, response, remission	Pts with TRD, age ≥ 18 yrs, bipolar or unipolar depression, HAMD, MADRS or BDI scales, not treated with rTMS before, RCT, reporting on efficacy in comparison to sham, pharmacological therapy, ECT or cognitive therapy or one type of rTMS vs another type of rTMS	Grunhaus 2003, Janicak 2002, Keshtkar 2011, Pridmore 2000a, Pridmore 2000b, Rosa 2006	n.a.–2014	9 (#4,5 no)

Author and year	Study type	Number of patients, number of RCTs	Aim of the study	Intervention(s) vs Comparison(s)	Main endpoints	Inclusion criteria	Included studies	Period searched	AMSTAR Score (# no, can't answer, not applicable)
Leggett, 2015 [85]	SR and MA	rTMS vs ECT: 205 pts, 6 RCTs	To establish the efficacy and optimal protocol for rTMS among adults and youth with TRD.	rTMS vs sham rTMS, rTMS vs ECT, HF rTMS vs LF rTMS, B-rTMS vs unilateral rTMS	Response, remission	*Inclusion:* TRD or pts who have had ≥ 2 previous treatments, age >18 yrs, bipolar or unipolar depression, HAMD, MADRS, BDI scales, not been treated with rTMS prior to the study, RCT	Grunhaus 2003, Janicak 2002, Kesthkar 2011, Pridmore 2000a, Pridmore 2000b, Rosa 2006	n.a.–2014	9 (#4,5 no)
Lepping, 2014 [83]	SR	rTMS vs ECT: 212 pts, 5 RCTs	To assess the clinical relevance of the reported efficacy of rTMS.	rTMS (HF, LF,B) vs sham rTMS, rTMs vs ECT	Standardized mean difference in depression scores	*Inclusion:* human subjects with depression irrespective of the subtype and criteria used, rTMS as mono- or add-on therapy, HAMD scale, RCTs or non-RCTs, published in peer-reviewed journal, full-text available, sample size for each study arm reported	Dannon 2000, Grunhaus 2003, Janicak 2002, Keshtkar 2011, Wang 2004	n.a.-2014	5 (#4,5,7,8,9, 10 no or can't answer)
Serafini, 2015 [87]	SR	rTMS vs ECT: 118 pts, 3 RCTs	Systematically investigate the role of rTMS in improving neurocognition in patients with TRD	rTMS vs sham rTMS, rTMS vs ECT, DTMS, rTMS of the anterior middle frontal gyrus vs sham rTMS, R-rTMS, L-rTMS	Depression severity, verbal memory and fluency, response and remission, working memory, attention, visuospatial memory	*Inclusion:* published in peer-reviewed journal, pts with TRD, analysis of the effect of neurocognitive functioning	McLoughlin 2007, Rosa 2006, Schulze-Rauschenbach 2005	1995-2014	4 (#4,5,7,8,9, 10,11 no)

Abbreviations: AMSTAR A MeaSurement Tool to Assess systematic Reviews, B bilateral, BDI Beck Depression Inventory, B-rTMS bilateral repetitive transcranial magnetic stimulation, CGI Clinical Global Impression, DLPFC dorsolateral prefrontal cortex, DTMS deep transcranial magnetic stimulation, ECT electroconvulsive therapy, HAMD Hamilton Depression Scale, HF high frequency, Hz Hertz, LF low frequency, L-rTMS left-side repetitive transcranial magnetic stimulation, MADRS Montgomery–Åsberg Depression Rating Scale, MDD major depressive disorder, pts patients, rTMS repetitive transcranial magnetic stimulation, R-rTMS right-side repetitive transcranial magnetic stimulation, RCT randomized controlled trial, SR systematic review, TRD treatment-resistant depression, yrs years

Evidence tables of individual studies included for clinical effectiveness and safety

Table A5: Characteristics of randomised controlled studies comparing rTMS with sham

Study characteristics						
Author, year, reference number	**Kang, 2016 [14]**	**Chen, 2013 [94]**	**Bakim, 2012 [51]**	**Blumberger, 2012 [65]**	**Fitzgerald, 2012 [72]**	**George, 2010 [52]**
Study Registration number (Registry identifier)	NCT01325831	N/A	N/A	NCT00305045	N/A	NCT00149838
Country	South Korea	Taiwan	Turkey	Canada	Australia	USA
Sponsor	Yonsei University College of Medicine	Tzu-Chi General Hospital, Tzu-Chi University, National Science Council	N/A	Ontario Mental Health Foundation, Canadian Institutes of Health Research, NHMRC, NARSAD	NHMRC	National Institute of Mental Health
Comparator	Sham	Sham	Sham	Sham	Sham and bilateral rTMS	Sham
Study design	RCT	RCT	RCT	RCT	RCT	Multisite RCT
Number of patients (active vs sham)	24 (13 vs 11)	20 (10 vs 10)	35 (23 vs 12)	46 (24 vs 22)	44 (24 vs 20)	190 (92 vs 98)
Study duration	2009-2011	Jan 2008 – Oct 2008	July 2007 – N/A	Jan 2006 – Jan 2009	Jan 2008 – Nov 2010	Oct 2004 – March 2009
Objectives	To investigate the thera-peutic effects of and the underlying neurobiological changes 2-week HF-rTMS on the left DLPFC in patients with TRD.	To measure the acute antidepressant effect of rTMS and to evaluate participants 1 month after completion of the treatment.	To investigate the efficacy of rTMS at two different intensities as an AD treatment to antidepressants in patients with TRD.	To compare the efficacy of bilateral rTMS with unilateral and sham rTMS and to evaluate the tolerability and side effects.	To investigate whether there is an advantage in efficacy of sequential bilateral rTMS compared to standard HF left sided rTMS.	To test whether daily left prefrontal rTMS safely and effectively treats major depressive disorder.
Model used	Magstim Rapid, figure 8 coil	Magstim	Magstim Rapid2	Medtronic rTMS, figure 8 coil	Medtronic Magpro30	Neuronetics Inc.

Study characteristics						
Author, year, reference number	**Kang, 2016 [14]**	**Chen, 2013 [94]**	**Bakim, 2012 [51]**	**Blumberger, 2012 [65]**	**Fitzgerald, 2012 [72]**	**George, 2010 [52]**
Inclusion criteria	MDD after DSM-IV-TR diagnostic criteria, current major depressive episode, failed to achieve adequate improvement (≤ 50% on HDRS-17) after at least 8 w of treatment with ≥ 1 SRRI	MDD patients failed to achieve adequate improvement (≤ 50% on HDRS-17) after ≥ 2 antidepressant treatments	Unipolar MDD, recurrent or single episode without psychotic features, age 18-65 yrs, right-handed, no response to adequate courses of ≥ 2 different classes of antidepressants, no change in the treatment regimen ≥ 4 w, scored ≥ 18 on HDRS-17 and ≥ 20 on MADRS	Age 18-85 yrs, DSM-IV diagnosis of MDD without psychotic features, TRD, ≥ 21 on HDRS, stable doses of psychotropic medications ≥ 4 w prior to randomization, capable to consent, currently outpatient	Diagnosis of moderate to severe depression (scoring >15 on HDRS-17)	Age 18-70 yrs, free of anti-depressant medication, DSM-IV diagnosis of MDD, current episode lasting < 5 yrs, ≥ 20 on HDRS, stable during 2 w free of medication, TRD
Exclusion criteria	Current or past history of psychotic disorder other than MDD (including anxiety disorder, substance use disorder), seizure, mental retardation, high risk of suicide, cognitive impairment (score <24 on the Mini-Mental State Examination), or contraindications for fMRI	High risk of suicide, any physical abnormality such as a head injury or epilepsy or if patients had an implanted pacemaker	Comorbidity of any other Axis I disorder, current or past history of epilepsy, head trauma, encephalitis, meningitis, or other cerebrovascular disease, pregnancy, pace-maker or medical pump implants, metal implant in the skull, any use of ECT, antipsychotics or anticonvulsants which may change the MT, inability to read in Turkish	DSM-IV substance dependence in the last 6 mo (excl. nicotine), substance abuse in the last month, borderline personality disorder or antisocial personality disorder, bipolar I, II or NOS, had significant unstable medical or neurologic illness or history of seizures, acutely suicidal, pregnant, metal implants in the cranium, dementia or a current MMSE score < 26, received benzodiazepines, MAOI, or buproprion during the previous 4 w, prior treat-ment with rTMS for any indication	Bipolar disorder, significant active medical/neurological illness, or contraindication to rTMS. Concurrent Axis I psychiatric disorders were not excluded, with the exception of schizophrenia spectrum disorders	Other Axis I disorders, failed to respond to ECT, pervious treatment with rTMS or VNS, family history of seizure, neurologic disorder, ferro-magnetic material in body or near head, pregnancy, taking medication which lowers seizure threshold, positive urine test for cocaine, marijuana, PCP or opiates
Add-on or monotherapy	Add-on	Add-on	Add-on	Add-on	Add-on	Mono
Follow-up duration	N/A	4 w	N/A	N/A	6 w[1]	6 w[1]
Loss-to-FU, n (%)	N/A	0	N/A	N/A	3 (12.5) vs 0	N/A
Depression scale used	HDRS-17	HDRS-17	HDRS-17, MADRS	HDRS-17	HDRS-17, MADRS	HDRS-24, MADRS

[1] After 3 week treatment, extension to 6 weeks

Study characteristics						
Author, year, reference number	**Kang, 2016 [14]**	**Chen, 2013 [94]**	**Bakim, 2012 [51]**	**Blumberger, 2012 [65]**	**Fitzgerald, 2012 [72]**	**George, 2010 [52]**
Frequency, Hz	10	20	20	10	10	10
Trains, n	20	20	20	29	30	75
Train duration, s	5	2	2	5	5	4
Inter-train interval, s	25	N/A	28	30	N/A	26
Pulses per session	1000	800	800	1450	1500	3000
Number of sessions (duration of intervention)	10 (2 w)	10 (2 w)	30 (6 w)	30 (6 w)	15 (3 w)	15 (3 w)
Total pulses	10000	8000	24000	21750	22500	45000
Unilateral/bilateral, side if unilateral	Unilateral, left DLPFC, 5 cm rule	Unilateral, left DLPFC, 5 cm rule	Unilateral, left DLPFC	Unilateral, left DLPFC	Unilateral, left DLPFC	Unilateral, left DLPFC
Intensity of the stimulation (% RMT)	110	90	80/110	100/120	120	120
Patient characteristics *(active vs sham)*						
Age, y mean (SD)	42.8 (19.1) vs 52.2 (20.1)	44.1 (4.4) vs 47.3 (3.5)	43.09 (8.18) vs 44.4 (10.2)	48.9 (13.4) vs 45.8 (13.4)	43.3 (12.7) vs 44.9 (15.7)	47.7 (10.6) vs 46.5 (12.3)
Sex, male/female, n	3/9 vs 1/8	3/7 vs 6/4	3/20 vs 1/11	12/14 vs 6/14	9/15 vs 12/8	34/58 vs 48/50
Previous therapy	All participants were taking antidepressants (SSRI) for > 8 w	≥ 2 antidepressant treatments	72.7% patients in the 110% group and 58.3% patients both in the 80% and sham groups used SNRIs, the rest used SSRIs	≥ 2 antidepressant treatments SSRI: 8 vs 3 SNRI: 3 vs 5 Tricyclic antidepressant: 5 vs 3 Mirtazapine: 2 vs 1 Trazodone: 2 vs 1 Lithium: 0 vs 1 Benzodiazepine: 9 vs 7 Atypical antipsychotics: 2 vs 1	≥ 2 antidepressant treatments. (mean number of courses across episodes 5.20±3.3)	1-4 or intolerant to ≥ 3

Study characteristics						
Author, year, reference number	**Kang, 2016 [14]**	**Chen, 2013 [94]**	**Bakim, 2012 [51]**	**Blumberger, 2012 [65]**	**Fitzgerald, 2012 [72]**	**George, 2010 [52]**
Depression score at baseline, mean (SD)	24.1 (6.4) vs 20.0 (4.6)	23.5 (1.9) vs 24.9 (1.9)	HDRS: 24.09 (2.77) vs 25.58 (3.82) MADRS: 27.81 (3.09) vs 28.75 (5.59)	26.0 (3.3) vs 25.2 (2.8)	HDRS: 23.7 (3.8) vs 22.9 (2.1) MADRS: 32.0 (4.6) vs 32.0 (3.5)	HDRS: 26.3 (5.0) vs 26.5 (4.8) MADRS: 29.5 (6.9) vs 29.8 (6.4)
QoL (SF-36, Q-LES-Q) at baseline	N/A	N/A	N/A	N/A	N/A	N/A
Suicidal ideation/suicide score at baseline	N/A	N/A	N/A	N/A	N/A	N/A
Outcomes						
Efficacy *(active vs sham)*						
Depression score at end of treatment and last FU, mean (SD)	*2 w:* 10.1 (3.8) vs 15.3 (4.3)	*2 w:* 9.6 (1.5) vs 12.3 (1.4) *4 w FU:* 9.8 (1.6) vs 16.4 (1.5)	*6 w:* HDRS: 11.64 (8.12) vs 19.5 (7.83) MADRS: 13.54 (8.35) vs 21.91 (8.42)	*6 w:* 20.3 (5.1) vs 18.9 (6.4)	*3 w:* HDRS: 19.6 (4.2) vs 22.6 (5.0) MADRS: 27.5 (6.0) vs 30.0 (6.2) *6 w FU:* HDRS: 13.0 (7.0) vs N/A MADRS: 18.6 (9.7) vs N/A	*3 w:* HDRS: 21.61 (9.26) vs 23.38 (7.43) MADRS: 24.59 (11.44) vs 27.75 (9.06) *6 w FU:* N/A
Response, n (%)	9 (75) vs 0	7 (70) vs 8 (80)	8 (73) vs 2 (17)	1 (4.5) vs 2 (10)	0 vs 1 (4)	13 (14) vs 5 (5)
Remission, n (%)	3 (25) vs 0	N/A	6 (55) vs 1 (8)	1 (4.5) vs 1 (5)	N/A	13 (14) vs 5 (5)
QoL (SF-36, Q-LES-Q) at end of treatment	N/A	N/A	N/A	N/A	N/A	N/A
Drop-out, n (%)	N/A	N/A	N/A	Drop-out due to lack of perceived benefit, inability to attend sessions: 8 (33.3) vs 3 (13.6)	Discontinuation of intervention due to withdrawal, mild worsening of symptoms and unable to tolerate travel: 0 vs 3 (15)	11 (12) vs 9 (9)
Suicidal ideation/ suicide score post-treatment	N/A	N/A	N/A	N/A	N/A	N/A
Safety*, n of pts (%) (active vs sham)*						
SADEs						

Study characteristics						
Author, year, reference number	**Kang, 2016 [14]**	**Chen, 2013 [94]**	**Bakim, 2012 [51]**	**Blumberger, 2012 [65]**	**Fitzgerald, 2012 [72]**	**George, 2010 [52]**
Seizure	N/A	N/A	0[2]	0[2]	0[2]	N/A
Transient cognitive impairment	N/A	N/A	0[2]	0[2]	0[2]	N/A
Induced currents circuits in implanted devices	N/A	N/A	N/A	N/A	N/A	N/A
ADEs						
Headache	N/A	N/A	4 (17.4) vs 1 (8.3)	1 (4.2) vs 0	N/A	29 (32) vs 23 (23)
Syncope (fainting)	N/A	N/A	N/A	N/A	N/A	5 (5) vs 4 (4)
Scalp discomfort	N/A	N/A	2 (8.7) vs 0	1 (4.2) vs 0	N/A	17 (18) vs 10 (10)
Pain	N/A	N/A	N/A	N/A	N/A	1 (1) vs 1 (1)
Facial twitching	N/A	N/A	N/A	N/A	N/A	0 vs 1 (1)
Vertigo	N/A	N/A	N/A	N/A	N/A	2 (2) vs 2 (2)
Device-related insomnia/drowsiness	N/A	N/A	N/A	1 (4.2) vs 0	N/A	7 (8) vs 10 (10)
Transient induction of hypomania	N/A	N/A	N/A	N/A	N/A	N/A
Mild confusion	N/A	N/A	N/A	N/A	N/A	N/A
Transient hearing loss/tinnitus	N/A	N/A	N/A	N/A	N/A	N/A
Other AEs						Worsening of depression/ anxiety: 6 (7) vs 8 (8) Gastrointestinal 6 (7) vs 3 (3) Muscle aches: 4 (4) vs 4 (4) Other: 18 (20) vs 15 (15)

[2] It is stated that no serious adverse event occurred, but not stated separately for seizure and cognitive impairment.

Study characteristics						
Author, year, reference number	**Stern, 2007 [50]**	**Triggs, 2010 [63]**	**Mogg, 2008 [71]**	**Bretlau, 2008 [58]**	**O'Reardon, 2007 [16] Solvason, 2014 [15]**	**Loo, 2007 [68]**
Study Registration number (Registry identifier)	N/A	NCT00711568	ISRCTN70121208	N/A	NCT00104611	N/A
Country	USA	USA	UK	Denmark	USA	Australia
Sponsor	Spanish Ministerio de Educacion y Cienca, Milton Found, Stanley Vada NAMI Foundation, National Alliance for Research in Schizophre-nia and Depression, NIHM	Veterans Affairs	Guy's and St Thomas' Charitable Foundation, NCCHTA, National Alliance for Research on Schizo-phrenia and Depression, Psychiatry Research Trust	Medicon Valley Academy, H Lundbeck A/S	Neuronetics Inc.	National Health and Medical Research Council Programme
Comparator	Sham, other rTMS protocols	Sham, other rTMS protocols	Sham	Sham	Sham	Sham
Study design	RCT	RCT	RCT	RCT	Multisite RCT	RCT
Number of patients (active vs sham)	25 (10 vs 15)	32 (18 vs 14)	59 (29 vs 30)	45 (22 vs 23)	301 (155 vs 146)	38 (19 vs 19)
Study duration	N/A	6 yrs	March 2002-Aug 2004	Apr 2003–Dec 2005	Jan 2004-Aug 2005	N/A
Objectives	To test if both HF left-sided and LF right-sided DLPFC stimulation have equivalent antidepressant effects.	To compare HF-rTMS of the left and right DLPFC with sham in a parallel group design.	To assess the efficacy of rTMS and report follow-up data and on the success of blinding.	To assess the efficacy of rTMS compared to sham and to compare results to Avery 2006 [64].	To test if rTMS over the left DLPFC is effective and safe in the acute treatment of MDD. Solvason 2014: To summarize the QoL outcomes of O'Reardon 2007 [16]	To test the efficacy and safety of twice-daily rTMS over 2 weeks.
Model used	Magpro, Magstim Super Rapid	Magstim Super Rapid, figure 8 coil	Magstim Super Rapid, figure 8 coil	Magstim Super Rapid, figure 8 coil	Neuretics Model 2100 Therapy System	Magstim Super Rapid, figure 8 coil
Inclusion criteria	Right-handed, age 21-80 yrs, MDD after SCID and DSM-IV criteria (score of 20 on the HDRS), no psychotic features, no other Axis I, naïve to TMS	Age 18-75 yrs, TRD according to DSM-IV criteria and verified by the SCID, total score ≥ 18 on HDRS-24, score ≥ 3 on item number 1 of the HDRS-24 in two separate screening sessions	Age >18 yrs, right-handed, diagnosis of MDD episode established by case-note review and confirmed by DSM-IV Axis I Disorders (SCID). Patients taking psychotropic medication were required to have been on a stable drug regimen for ≥ 4 w before study entry and to remain on the same medication during the study	Age 18-75 yrs, DSM-IV diagnosis of current MDD, TRD	Medication free outpatient, age 18-70 yrs, DSM-IV diagnosis of MDD, <3 yrs length of current episode, ≥4 CGI, ≥20 on HDRS, symptom stability for 1 w, TRD	DSM-IV diagnosis of MDD < 2 yrs in length, ≥25 on the MADRS, TRD

Study characteristics						
Author, year, reference number	**Stern, 2007 [50]**	**Triggs, 2010 [63]**	**Mogg, 2008 [71]**	**Bretlau, 2008 [58]**	**O'Reardon, 2007 [16] Solvason, 2014 [15]**	**Loo, 2007 [68]**
Exclusion criteria	History of schizophrenia, schizoaffective disorder, bipolar, obsessive compulsive disorder, personality disorder; substance abuse (except nicotine) within past year, current acute or chronic medical condition requiring treatment with psychoactive medication, history or family history of epilepsy, prior brain surgery, metal in the head, implanted device, pregnancy, or unable to tolerate medication withdrawal (14-day washout period)	History of schizophrenia, schizoaffective disorder, other functional psychosis, bipolar, alcohol or drug abuse within the past year, positive drug test, axis II Cluster A or Cluster B personality disorder or mental retardation, use of medications that may lower seizure threshold, history of epilepsy, intracranial tumour, major head trauma, central nervous system disease, implanted pacemaker or medication pump, metal plate in skull, need for rapid clinical response due to psychosis, or suicidality, use of anticonvulsant mood stabilizers, or inability to consent	History of seizures, head injury with loss of consciousness, brain surgery, presence of metallic implants, dementia or other Axis I diagnosis, substance dependency or abuse within the previous 6 m, previous rTMS treatment, inability to provide informed consent	Organic brain disorder, substance abuse, severe anxiety disorder, personality disorder, history of epilepsy, metal implants in head or neck, pacemaker, suicidal ideation (score of > 2 on the suicide item of HDRS), those receiving anti-psychotics, current episode > 24 mo, risk factors deterring escitalopram treatment, pregnancy	Psychosis, bipolar disorder, obsessive compulsive disorder, posttraumatic stress disorder, eating disorder, no response to ECT, prior treatment with TMS, pregnant, personal or family history of seizures, neurologic disorder or medication that alters seizure threshold, ferromagnetic material in close proximity to head	Axis I disorder, neurological illness, epilepsy, severe medical illness, implanted electronic devices, suicidal, or psychotic, patients failed >2 classes of antidepressants or a failed ECT
Add-on or monotherapy	Mono	Add-on	Add-on	Mono	Mono	Add-on
Follow-up duration	4 w[3]	3 mo	4 mo	3 mo	6 mo	6 w[4]
Loss-to-FU, n (%)	0	3 (6)	4 (7)	1 (0.5) vs 5 (21.7)	56 (36) vs 125 (86)	1 (10) vs 4 (33)
Depression scale used	HDRS-21	HDRS-24	HDRS-17	HDRS-17	HDRS-17/24, MADRS	HDRS-17, MADRS
Frequency, Hz	10	5	10	8	10	10
Trains, n	20	50	20	20	75	30
Train duration, s	8	8	5	8	4	5
Inter-train interval, s	52	22	55	52	26	25

[3] After 2 weeks treatment, extension to 4 weeks

[4] After 2 weeks treatment, extension to 6 weeks

Study characteristics						
Author, year, reference number	**Stern, 2007 [50]**	**Triggs, 2010 [63]**	**Mogg, 2008 [71]**	**Bretlau, 2008 [58]**	**O'Reardon, 2007 [16] Solvason, 2014 [15]**	**Loo, 2007 [68]**
Pulses per session	1600	2000	1000	1280	3000	1500
Number of sessions (duration of intervention)	10 (2 w)	10 (2 w)	10 (2 w)	15 (3 w)	30 (6 w)	20 (2 w)
Total pulses	16000	20000	10000	19200	90000	30000
Unilateral/bilateral, side if unilateral	Unilateral, left DLPFC	Unilateral, left DLPFC, 5 cm rule	Unilateral, left DLPFC	Unilateral, left DLPFC	Unilateral, left DLPFC, 5 cm rule	Unilateral, left DLPFC
Intensity of the stimulation (% RMT)	110	100	110	90	120	110
Patient characteristics *(active vs sham)*						
Age, y mean (SD)	53.2 (12.0) vs 53.3 (9)	46.7 (15.3) vs 41.9 (14.1)	55.0 (18.0) vs 52.0 (15.5)	53.1 (10.1) vs 57.8 (10)	47.0 (11.0) vs 48.7 (10.6)	49.8 (2.5) vs 45.7 (15)
Sex, male/female, n	4/6 vs 6/9	4/14 vs 8/6	13/16 vs 9/21	7/15 vs 13/10	69/86 vs 72/74	9/10 vs 11/8
Previous therapy	≥ 1 previous treatment (including ECT)	≥ 2 separate trials of antidepressants including at least one SSRI or intolerant to ≥ 3 including at least one SSRI	≥ 2 treatments: 22 vs 24 ≥ 3 treatments: 15 vs 16 treatment with ECT: 7 vs 10 medications: SSRI (10 vs 7), tricyclic (9 vs 9), MAOI (0 vs 1), venlafaxine (10 vs 7), lithium (0 vs 4), antipsychotic (2 vs 6), benzodiazepine (2 vs 6), zopiclone (5 vs 7), no medication (2 vs 4)	≥ 1 previous treatment ECT: 1 vs 2	≥ 1 previous treatment	≥ 1 previous treatment, but maximum 2 failed treatments
Depression score at baseline, mean (SD)	27.8 (3.2) vs 27.4 (2.9)	28.2 (6.0) vs 27.5 (3.0)	20.5 (4.4) vs 21.6 (4.7)	25.3 (3.0) vs 24.7 (3.2)	HAMD-17: 22.6 (3.3) vs 22.9 (3.5)	HAMD-17: 19.2 (3.7) vs 20.9 (4.2) MADRS: 29.5 (3.9) vs 32.6 (4.3)

Study characteristics						
Author, year, reference number	**Stern, 2007 [50]**	**Triggs, 2010 [63]**	**Mogg, 2008 [71]**	**Bretlau, 2008 [58]**	**O'Reardon, 2007 [16] Solvason, 2014 [15]**	**Loo, 2007 [68]**
QoL (SF-36 PF, SF-36 general health, SF-36 mental health, bodily pain, vitality, Q-LES-Q) at baseline	N/A	N/A	N/A	N/A	*SF-36 PF:* 45.9 (10.5) vs 43.2 (11.3) *SF-36 gen. health:* 41.1 (9.8) vs 40.9 (9.5) *SF-36 mental h.:* 25.1 (8.7) vs 24.6 (7.8) *Q-LES-Q total score:* 37.6 (8.2) vs 36.5 (7.9)	N/A
Suicidal ideation/ suicide score at baseline	N/A	N/A	N/A	N/A	N/A	N/A
Outcomes						
Efficacy *(active vs sham)*						
Depression score (at end of treatment and FU), mean (SD)	*2 w:* 15.1 (6) vs 26.7 (3.6) *4 w FU:* 13.4 (5.6) vs 26.8 (2.3)	*2 w*: 19.8 (9.1) vs 17.7 (10.4) *3 mo FU*: 16.3 (11.5) vs 17.9 (11.6)	*2 w*: 17.1 vs 18.8 *4 mo FU*: 19.8 vs 15.1	*3 w:* 16.4 (4.5) vs 19.1 (4.8) *3 mo FU:* 11.1 (6.7) vs 13.5 (7.2)	*6 w:* 17.1 (7.7) vs 19.6 (7.0) *6 mo FU*: N/A	*2 w:* HAMD-17: 11.8 (5.7) vs 15.4 (7.3) MADRS: 18.9 (7.7) vs 27.1 (10.2) *6 w FU:* N/A
Response, n (%)	*2 w:* 5 (50) vs 0 *4 w FU:* 4 (40) vs 0	*2 w*: 4 (22) vs 6 (43) *3 mo FU*: 6 (33) vs 4 (29)	*2 w*: 9 (32) vs 3 (10) *4 mo FU:* N/A	N/A	*6 w:* 38 (24.5) vs 20 (13.6) *6 mo FU*: N/A	2 w: 6 (32) vs 3 (16) *6 w FU:* N/A
Remission, n (%)	*2 w:* 3 (33) vs 0 *4 w FU:* 4 (40) vs 0	N/A	*2 w:* 7 (25) vs 3 (10) *4 mo FU:* N/A	N/A	*6 w:* 24 (15.5) vs 13 (8.9) *6 mo FU:* N/A	2 w: 3 (16) vs 2 (11) *6 w FU:* N/A

Study characteristics						
Author, year, reference number	**Stern, 2007 [50]**	**Triggs, 2010 [63]**	**Mogg, 2008 [71]**	**Bretlau, 2008 [58]**	**O'Reardon, 2007 [16] Solvason, 2014 [15]**	**Loo, 2007 [68]**
QoL (SF-36 PF, SF-36 general health, SF-36 mental health, bodily pain, vitality, Q-LES-Q,), mean difference (SD)	N/A	N/A	N/A	N/A	*SF-36 PF:* *6 w:* 47.3 (9.6) vs 44.6 (10.5) *6 mo:* 48.8 (10.4) vs 49.8 (8.1) *SF-36 gen. health:* *6 w*: 42.6 (10.1) vs 40.9 (10.1) *6 mo*: 45.5 (11.1) vs 44.8 (13.1) *SF-36 mental h.:* *6 w:* 30.5 (13.0) vs 27.1 (11.7) *6 mo:* 43.8 (11.3) vs 41.1 (11.9) *Bodily pain scores* 6 w: 45.6 (10.2) vs 46.3 (9.3) 6 mo: 47.5 (8.9) vs 51.3 (6.8) *Vitality scores* 6 w: 38.1 (10.6) vs 38.2 (11.5) 6 mo: 45.0 (11.1) vs 44.3 (15.3) *Q-LES-Q score:* *6 w:* 42.4 (12.3) vs 39.3 (10.2) *6 mo:* 56.0 (11.3) vs 55.3 (12.2)	N/A
Drop-out, n (%)	0 vs 3 (20) withdrew due to AEs (headache)	N/A	0 vs 2 (7) withdrew due to AEs (tinnitus)	0 vs 0	7 (4) vs 9 (6) (AE 4 vs 4, failed to return 1 vs 0, unsatisfactory response 1 vs 2, patient request unrelated to study 1 vs 1, other issues 0 vs 2)	1 (5) vs 1 (5) withdrew due to very depressed and attendance stressful, could not attend
Suicidal ideation/ suicide score post-treatment	N/A	N/A	N/A	N/A	0 vs 1 (0.7)	N/A
***Safety**, n pts (active vs sham)*						
SADEs						
Seizure	0	N/A	0	N/A	0	0

Study characteristics						
Author, year, reference number	**Stern, 2007 [50]**	**Triggs, 2010 [63]**	**Mogg, 2008 [71]**	**Bretlau, 2008 [58]**	**O'Reardon, 2007 [16] Solvason, 2014 [15]**	**Loo, 2007 [68]**
Transient cognitive impairment	N/A	0 vs 1 (7)	N/A	*UKU scores*[5] *at 3 mo:* 0 vs 0	N/A	N/A
Induced currents circuits in implanted devices	N/A	N/A	N/A	N/A	N/A	N/A
ADEs						
Headache	9 in total	7 (39) vs 6 (43)	N/A	*UKU scores at 3 mo*: 0.1 (0.3) vs 0.06 (0.24)	59 (36) vs 6 (4)[6]	8 (42) vs 0
Syncope (fainting)	N/A	5 (28) vs 2 (14)	N/A	N/A	N/A	N/A
Scalp discomfort	N/A	6 (33) vs 3 (21)	N/A	N/A	18 (12) vs 2 (1)	15 (79) vs 0
Pain	N/A	1 (6) vs 0	N/A	N/A	59 (38) vs 6 (4)	N/A
Facial twitching	N/A	1 (6) vs 0	N/A	N/A	11 (7) vs 5 (3)	3 (16) vs 0
Vertigo/dizziness	N/A	3 (17) vs 2 (14)	0 vs 2 (7)	N/A	N/A	N/A
Device-related insomnia/drowsiness	N/A	1 (6) vs 1 (7)	N/A	*UKU scores at 3 mo:* 0.24 (0.44) vs 0.39 (0.61)	N/A	N/A
Transient induction of hypomania	N/A	N/A	N/A	N/A	N/A	1 (5) vs 0
Mild confusion	N/A	N/A	N/A	N/A	N/A	N/A
Transient hearing loss/tinnitus	N/A	N/A	0 vs 2 (7)	N/A	N/A	N/A
Other AEs	0	Neck muscle soreness: 1 (6) vs 0 Nausea: 4 (22) vs 0	N/A	*UKU scores at 3 mo*: Nausea: 0.05 vs 0.17 Diarrhea: 0.1 vs 0 Dry mouth: 0.14 vs 0.11 Palpitations: 0.14 vs 0.12	N/A	Tearfulness: 4 (21) vs 0 Nausea: 0 vs 1 (5) Agitation: 1 (5) vs 0 Feeling high: 1 (5) vs 0

[5] Used for the assessment of side effects of psychopharmacological medications. 48 symptoms are rated in 4 categories.

[6] Referred to as application site pain in the study

Study characteristics						
Author, year, reference number	**Avery, 2006 [64]**	**Su, 2005 [53]**	**Holtzheimer, 2004 [57]**	**Mosimann, 2004 [55]**	**Fitzgerald, 2003 [56]**	**Hoppner, 2003 [95]**
Study Registration number (Registry identifier)	NA	NA	NA	NA	NA	NA
Country	USA	Taiwan	USA	Germany	Australia	Germany
Sponsor	National Insitute of Mental Health	Taipei Veterans General Hospital	University of Washington	Swiss National Science Foundation	National Health and Medical Research Council, Stanley Medical Research Insitute	NA
Comparator	Sham	Sham	Sham	Sham	LF-rTMS/sham	LF-rTMS/sham
Study design	RCT	RCT	RCT	RCT	RCT	RCT
Number of patients (active vs sham)	68 (35 vs 33)	30 (20 vs 10)	15 (7 vs 8)	24 (15 vs 9)	60 (20 in each group)	30 (10 in each group)
Study duration	Jan 2001 – Febr 2004	N/A	Jan 1998 – Dec 1999	N/A	Oct 2000 – Sept, 2002	N/A
Objectives	To assess if patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation.	To determine whether lelft DLPFC rTMS can alleviate TRD in Chinese patients and to investigate what demographic variables or clinical features may predict better response.	To determine if rTMS would have greater antidepressant effects than sham stimulation and that rTMS would be safe and tolerable.	To assess the effect of rTMS in older outpatients with TRD.	To prospectively evaluate the efficacy of HF-TMS and LF-TMS in TRD and compared with a sham treated control group.	To compare clinical effects of two different stimulation procedures with sham stimulation as add-on treatments in patients with depressive disorders.
Model used	Magpro Compact, MagPro X100, Magpro R30, figure 8 coil	MAGSTIM Rapid II, MAGSTIM Model 2002, Neurosign Model 4000, figure 8 coil	Magpro Compact, MagPro X100, Magpro R30, figure 8 coil	MAGSTIM Rapid II, MAGSTIM Model 2002, Neurosign Model 4000, figure 8 coil	MAGSTIM Rapid II, MAGSTIM Model 2002, Neurosign Model 4000, figure 8 coil	Maglite r 25, figure 8 coil
Inclusion criteria	Age 21-65 yrs, current MDD as diagnosed by DSM-IV, TRD (failed to tolerate $\geq$ 2 antidepressant trials, score $\geq$ 17 on HDRS	Patients who met the DSM-IV criteria for a major depressive episode or bipolar disorder (based on the Mini-International Psychiatric Interview), TRD	Age 21-65 yrs, right handed, MDD as diagnosed by DSM-IV, no major psychiatric or medical comorbidity, TRD, score $\geq$ 18 on HDRS, not on medication	Age 40-90 yrs, diagnosis of TRD according to DSM-IV and ICD-10	N/A	Depressive, right-handed in-patients

Study characteristics						
Author, year, reference number	**Avery, 2006 [64]**	**Su, 2005 [53]**	**Holtzheimer, 2004 [57]**	**Mosimann, 2004 [55]**	**Fitzgerald, 2003 [56]**	**Hoppner, 2003 [95]**
Exclusion criteria	Prior rTMS, bipolar disorder, failure of ≥ 9 ECT, substance abuse or addiction in past 2 yrs, antisocial or borderline personality disorder, psychosis, seizure disorder, closed head injury with loss of consciousness, brain surgery, major psychiatric or medical comorbidity	History of epilepsy, history of physical or neurological abnormalities, implanted pacemaker, substantial risk of suicide during the trial, previously had major head trauma or displayed any psychotic symptoms, previously had rTMS or ECT	History of bipolar disorder, failure to respond to ECT therapy, history of substance abuse, psychosis, pregnancy	Head injury, epilepsy, comorbid unstable medical or neurological illness, no birth control (women)	Significant medical illness, neurologic disorders or other Axis I psychiatric disorders	Patients with other relevant medical illness were excluded.
Add-on or monotherapy	Add on + Mono	Add on	Mono	Add on	Add on	Add on
Follow-up duration	6 mo	2 w	1 w (cross-over)	N/A	2 w (cross-over)	N/A
Loss-to-FU, n (%)	N/A	3 (33)	2 active vs. 1 sham	N/A	1	N/A
Depression scale used	HDRS-17	HDRS-21, BDI, CGI	HDRS-17, BDI	HDRS-21, BDI	MADRS	HDRS-21
Frequency, Hz	10	5 and 20	10	20	10	20
Trains, n	32	40	32	40	20	20
Train duration, s	5	8s, 2 s	5	2	5	2
Inter-train interval, s	25-30	N/A	30-60	25	25	30
Pulses per session	1600	1600	1600	1600	1000	800
Number of sessions (duration of intervention)	15 (3 w)	10 (2 w)	10 (2 w)	10 (2 w)	10 (2 w)	10 (2 w)
Total pulses	24000	16000	16000	16000	10000	8000
Unilateral/bilateral, side if unilateral	Unilateral, left DLPFC	Unilateral, left DLPFC	Unilateral, left DLPFC	Unilateral, left DLPFC	Unilateral, left or right DLPFC	Unilateral, left or right DLPFC, 5 cm rule
Intensity of the stimulation (% RMT)	110	100	110	100	100	90
Patient characteristics *(active vs sham)*						
Age, y mean (SD)	44.3 (10.3) vs 44.2(9.7)	5Hz: 43.2(10.6) 20Hz: 43.6 (12) Sham: 42.6 (11)	40.4(8.5) vs 45.4(4.9)	60 (13.4) vs 64.4(13.0)	45.55 (11.45) vs 49.5(11.24)	60.36 (2.12) vs 52 (3.69)

Study characteristics						
Author, year, reference number	**Avery, 2006 [64]**	**Su, 2005 [53]**	**Holtzheimer, 2004 [57]**	**Mosimann, 2004 [55]**	**Fitzgerald, 2003 [56]**	**Hoppner, 2003 [95]**
Sex, male/female, n	14/21 vs 17/16	5Hz: 3/7 20Hz: 2/8 Sham: 3/7	3/4 vs 5/3	10/5 vs 4/5	13/7 vs 9/11	3/8 vs 3/6
Previous therapy	≥2 failed trials of antidepressants History of positive ECT response: 3 vs 4 Total number of medication trials: 8.23 vs 8.91	≥2 failed trials of antidepressants	≥2 failed trials of antidepressants	≥2 failed trials of antidepressants	≥2 failed trials of antidepressants	≥1 failed trials of anti-depressants (incl. doxepin, trimipramine, mirtazapine, clomipramine, venlafaxine, maprotiline, mianserin etc.)
Depression score at baseline, mean (SD)	23.5(3.9) vs 23.5(2.9)	5Hz: 26.5(5.2) 20Hz: 23.2(7.5) Sham: 22.7 (4.7)	22.7(5.3) vs. 20.8 (6.3)	28 (4.6) vs 24.5 (7.3)	36.1 (7.5) vs 35.75 (8.14)	N/A
QoL (SF-36, Q-LES-Q) at baseline	N/A	N/A	N/A	N/A	N/A	N/A
Suicidal ideation/ suicide score at baseline	N/A	N/A	N/A	N/A	N/A	N/A
Outcomes						
Efficacy *(active vs sham)*						
Depression score at end of treatment and last FU, mean (SD)	15.7 vs 19.8 *6 mo FU:* 4.6 (2.7) vs N/A	5Hz: 14.2(6.0) vs 12.3 (7.7) 20Hz: 13.4(4.9) vs 9.8 (7.1) Sham: 3.7 (9.3) vs 19.0 (7.7)	2 w: 14.6 (3.2) vs 15.3 (3.0) *1 w FU:* 18.8 (2.5) vs 17.6 (2.1)	23.3 (7.2) vs. 20.4 (6.6)	30.8 (7.5) vs 35.4 (7.5)	N/A
Response, n (%)	11 (31) vs 2 (6) *6 mo FU*: 5 vs 1 (relapse at 6 mo: 6 vs 1)	12 (60) vs 1 (10)	2 w: 2 (29) vs 1 (13) *1 w FU:* 0 vs 0 (relapse at 1 w: 2 vs 1)	1 (6.6) vs 0	0 vs 0[7]	5 (50) vs 5 (50)
Remission, n (%)	7 (20) vs 1 (3)	10 (50) vs 0	N/A	N/A	0 vs 0	N/A
QoL (SF-36, Q-LES-Q at end of treatment, mean SD)	N/A	N/A	N/A	N/A	N/A	N/A

[7] The study defined response as >20% decrease on MADRS and reported response 8 (40) vs 2 (10). When applying the >50% decrease as the other studies the response is 0 in each groups.

Study characteristics						
Author, year, reference number	**Avery, 2006 [64]**	**Su, 2005 [53]**	**Holtzheimer, 2004 [57]**	**Mosimann, 2004 [55]**	**Fitzgerald, 2003 [56]**	**Hoppner, 2003 [95]**
Drop-out, n (%)	0 vs 0	0 vs 1 (10) (due to worsening of depression symptoms)	N/A	N/A	0	1 (10) vs 0 (due to headache and insufficient effectiveness)
Suicidal ideation/suicide score post-treatment	N/A	N/A	N/A	1 (6.6) vs 0	N/A	N/A
***Safety**, n pts (active vs sham)*						
SADEs						
Seizure	0 vs 0	N/A	N/A	N/A	N/A	N/A
Transient impairment of working memory	N/A	N/A	N/A	N/A	N/A	N/A
Induced currents circuits in implanted devices	N/A	N/A	N/A	N/A	N/A	N/A
ADEs						
Headache	11 (31) vs 1 (3)	4 (20) vs 1 (10)	N/A	0 vs 2 (22)	6 (10) in total	N/A
Syncope (fainting)	N/A	N/A	N/A	N/A	N/A	N/A
Scalp discomfort	N/A	N/A	N/A	N/A	7 (11) in total	N/A
Pain	N/A	N/A	N/A	N/A	7 (11) in total	N/A
Facial twitching	N/A	N/A	N/A	N/A	N/A	N/A
Vertigo	1 (3) vs 0	N/A	N/A	0 vs 1 (6.7)	1 (5) vs 1 (5)	N/A
Device-related insomnia/Drowsiness	N/A	N/A	N/A	N/A	N/A	N/A
Transient induction of hypomania	N/A	1 vs 0 (in the open label phase, the pt was bipolar)	N/A	N/A	0	N/A
Mild confusion	0 vs 0	N/A	N/A	N/A	N/A	N/A
Transient hearing loss	N/A	N/A	N/A	N/A	N/A	N/A
Other AEs	N/A	N/A	N/A	N/A	N/A	N/A

Study characteristics						
Author, year, reference number	**Boutros, 2002 [62]**	**Padberg, 2002 [49]**	**Garcia-Toro, 2001 [66]**	**Berman, 2000 [69]**	**Loo, 1999 [67]**	**Avery, 1999 [70]**
Study Registration number (Registry identifier)	N/A	N/A	N/A	N/A	N/A	N/A
Country	USA	Germany	Spain	USA	Australia	USA
Sponsor	VA MERIT and K24DA00520-01AA awards	German Federal Research Ministry	N/A	VA Merit Award (NNB), NIMH, State of Connecticut	Australian National Health and Medical Research Council Mood Disorders Unit, private donations	N/A
Comparator	Sham	Sham	Sham	Sham	Sham	Sham
Study design	RCT	RCT	RCT	RCT	RCT	RCT
Number of patients (active vs sham)	21 (12 vs 9)	30 (20 vs 10)	35 (17 vs 18)	20 (10 vs 10)	18 (9 vs 9)	6 (4 vs 2)
Study duration	N/A	N/A	N/A	N/A	N/A	N/A
Objectives	To provide additional efficacy and safety data for use of subthreshold rTMS as an augmentation strategy in TRD patients without any modifications on their current pharmacological therapy.	To investigate whether the antidepressant efficacy of rTMS may be related to the stimulation intensity applied.	To clarify the role played by the HF-rTMS applied on the left DLPC as a coadjuvant to psycho-pharmacological treatment of TRD.	To assess the efficacy of rTMS in unmedicated, TRD patients who meet criteria for major depression.	The efficacy and safety of left DLPFC rTMS for treating TRD were examined.	To present preliminary efficacy and safety of HF-rTMS delivered to TRD pts compared to sham.
Model used	MAGSTIM Rapid II, MAGSTIM Model 2002, Neurosign Model 4000, figure 8 coil	MAGSTIM Rapid II, MAGSTIM Model 2002, Neurosign Model 4000, figure 8 coil	Magpro Compact, MagPro X100, Magpro R30, figure 8 coil	Cadwell stimulator	MAGSTIM Rapid II, MAGSTIM Model 2002, Neurosign Model 4000, figure 8 coil	Cadwell stimulator
Inclusion criteria	Diagnosis of MDD, TRD, score ≥ 20 on HDRS	Patients who met the DSM-IV criteria for MDD	Age ≥ 18 yrs, DSM-IV diagnosis of unipolar MDD, TRD, right-handed	Age 18-70 yrs, met DSM-IV criteria for MDD, TRD, no diagnosis of substance or alcohol abuse, no history of neurologic illness	MDD as diagnosed by DSM-IV, TRD, ≥25 on MADRS	MDD as diagnosed by DSM-IV criteria, or bipolar disorder depressed phase, failed ≥ 2 antidepressant trials in the current episode, no proconvulsant medications, on stable medication or no medication for ≥6 w before the study, right-handedness, ≥ 20 on SIGH-SAD

Study characteristics						
Author, year, reference number	**Boutros, 2002 [62]**	**Padberg, 2002 [49]**	**Garcia-Toro, 2001 [66]**	**Berman, 2000 [69]**	**Loo, 1999 [67]**	**Avery, 1999 [70]**
Exclusion criteria	Suicidal ideations, prominent psychotic symptoms, history of neurological disorder, history of drug abuse within the past 3 mo	Patients with organic brain disorders, pacemakers, mobile metal implants or implanted medication pumps	History of seizures or neurosurgery, serious or uncontrolled medial illness, pacemaker or hearing aid, pregnancy, women of childbearing potential lacking effective contra-ceptive, high suicidal risk	Pregnancy, EEG abnormality suggestive of epileptic predisposition, significant unstable medical illness	Major physical or neurological abnormalities, treated with ECT during this depressive episode	Metal in the body, cardiac pacemaker, implanted electronic device, history of head injury associated with loss of consciousness, brain surgery, epilepsy, active suicidal intent, other major psychiatric or medical illnesses
Add-on or monotherapy	Add on	Add on	Add on	Mono	Add on	Add on
Follow-up duration	5 mo	N/A	1 mo	2 mo	1 mo	2 w
Loss-to-FU, n (%)	6 (50) vs 7 (78)	N/A	1 (6) vs 1 (6) (cross-over)	0 vs 3 (30)	2 (14) in total	0 vs 0
Depression scale used	HDRS-25	HDRS-21, MADRS	HDRS-21, HARS, CGI, BDI	HDRS-25, BDI, HARS	HDRS, MADRS, BDI	HDRS-21, BDI, CGI
Frequency, Hz	20	10	20	20	10	10
Trains, n	20	15	30	20	30	20
Train duration, s	2	10	2	2	5	5
Inter-train interval, s	58	30	20-40	58	30	55
Pulses per session	800	1500	1200	800	1500	1000
Number of sessions (duration of intervention)	10 (2 w)	10 (2 w)	10 (2 w)	10 (2 w)	10 (2 w)	10 (2 w)
Total pulses	8000	15000	12000	8000	1500	10000
Unilateral/bilateral, side if unilateral	Unilateral, left DLPFC	Unilateral, left DLPFC	Unilateral, left DLPFC, 5 cm rule	Unilateral, left DLPFC, 5 cm rule	Unilateral, left DLPFC	Unilateral, left DLPFC, 5 cm rule
Intensity of the stimulation (% RMT)	80	100/90	90	80	110	80
Patient characteristics *(active vs sham)*						
Age, y mean (SD)	49.5(8) vs 52(7)	100% 62.1 (4.6) 90% 60.3 (4.11) sham 52.7 (5.7))	51.5 (15.9) vs 50.0 (11)	45.2 (83) vs 39.4 (3.4)	45.7(14.7) vs 50.9 (14.7)	44.25 vs 45
Sex, male/female, n	8/4 vs 8/1	7/13 vs 2/8	10/7 vs 10/8	8/2 vs 6/4	N/A	N/A

Study characteristics						
Author, year, reference number	**Boutros, 2002 [62]**	**Padberg, 2002 [49]**	**Garcia-Toro, 2001 [66]**	**Berman, 2000 [69]**	**Loo, 1999 [67]**	**Avery, 1999 [70]**
Previous therapy	≥2 failed trials of antidepressants (incl. venlafaxine, mirtazapine, valproic, etc.)	≥2 failed trials of anti-depressants (incl. tricyclics, SSRI, MAOI, mirtazapine, venlafaxine, lithium, benzodiazepines, etc.)	≥2 failed trials of antidepressants	≥1 failed trials of antidepressants (incl. ECT)	≥2 failed trials of antidepressants	≥2 failed trials of antidepressants (incl. lorazepam, tranylcypromine)
Depression score at baseline, mean (SD)	34.4 (10.1) vs 31.7 (4.9)	100%: 23.6 (1.9) 90%: 21.9 (1.8) Sham: 24.4 (2.1)	27.11 (6.65) vs 25.6 (4.92)	37.1 (9.7) vs 37.3 (8.4)	N/A	21.3 (6.7) vs 19.5 (8.1)
QoL (SF-36, Q-LES-Q) at baseline	N/A	N/A	N/A	NA	N/A	N/A
Suicidal ideation/suicide score at baseline	N/A	N/A	N/A	NA	N/A	N/A
Outcomes						
Efficacy *(active vs sham)*						
Depression score at end of treatment and last FU, mean (SD)	N/A (the difference compared to baseline is reported) *5 mo FU: 18 vs N/A*	N/A	HDRS: 18.94 (7.69) vs 23.55 (6.07)	HDRS: *2 w:* 24.6 (9.22) vs 36.4 (9.05) *2 mo FU*: N/A	N/A	HDRS: *2 w:* 10.8 (3.5) vs 15.0 (2.5) *2 w FU*: 13.5 (10.8) vs 13.5 (5.9)
Response, n (%)	3 (25) vs 2 (22)	5 (25) vs 0	5 (29) vs 1 (6)	1 (10) vs 0 *2 mo FU:* 1 (10) vs 0	N/A	N/A
Remission, n (%)	N/A	3 (33) vs 0	N/A	NA	N/A	N/A
QoL (SF-36, Q-LES-Q at end of treatment or last FU, mean SD)	N/A	N/A	N/A	NA	N/A	N/A
Drop-out, n (%)	0 vs 1 (11)	1 in total	3 (18) vs 2 (11)	0 vs 3 (30) (due to lack of response)	0 vs 0	0 vs 0
Suicidal ideation/suicide score post-treatment	N/A	N/A	N/A	N/A	N/A	N/A
Safety*, n pts (%) (active vs sham)*						
SADEs						
Seizure	N/A	0 vs 0	N/A	N/A	0 vs 0	0 vs 0

Study characteristics						
Author, year, reference number	**Boutros, 2002 [62]**	**Padberg, 2002 [49]**	**Garcia-Toro, 2001 [66]**	**Berman, 2000 [69]**	**Loo, 1999 [67]**	**Avery, 1999 [70]**
Transient impairment of working memory	5 (42) vs 0	N/A	N/A	NA	N/A	N/A
Induced currents circuits in implanted devices	N/A	N/A	N/A	NA	N/A	N/A
ADEs						
Headache	N/A	2 in total	6 (33) vs N/A	6 (60) vs 5 (50)	3 (33) vs 0	N/A
Syncope (fainting)	N/A	N/A	N/A	NA	N/A	N/A
Scalp discomfort	3 (25) vs 1(11)	N/A	6 (33) vs N/A	NA	N/A	N/A
Pain	N/A	N/A	N/A	NA	N/A	4 (100) vs 2 (100)
Facial twitching	N/A	N/A	N/A	NA	N/A	NA
Vertigo	N/A	N/A	N/A	NA	N/A	NA
Device-related insomnia/Drowsiness	N/A	N/A	N/A	NA	N/A	NA
Transient induction of hypomania	N/A	N/A	N/A	NA	N/A	N/A
Mild confusion	N/A	N/A	N/A	N/A	N/A	N/A
Transient hearing loss	1 (8) vs 0	N/A	N/A	N/A	1 (11) vs 0	N/A
Other AEs	Diarrhoea: 1 (8) vs 0	Migraine: 0 vs 1 (10) Aversive tactile artefact: 5 (25) vs 0	N/A	N/A	N/A	N/A

Abbreviations: AE adverse event, ADE adverse device effect, BDI Beck Depression Inventory, CGI Clinical Global Impression, DLPFC dorsolateral prefrontal cortex, DSM-IV-TR Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, text revision, ECT electroconvulsive therapy, EEG electroencephalography, fMRI functional magnetic resonance imaging, FU follow-up, HARS Hamilton Anxiety Rating Scale, HDRS Hamilton Depression Rating Scale, HF high-frequency, Hz Hertz, LF low-frequency, MADRS Montgomery–Åsberg Depression Rating Scale, MDD major depressive disorder, MAOI monoamine oxidase inhibitors, MT motor threshold, mo month, n number, N/A not available, NAMI National Alliance on Mental Illness, NARSAD National Alliance for Research on Schizophrenia and Depression, NCCHTA National Coordinating Centre for Health Technology Assessment, NHMRC National Health and Medical Research Council, NIHM National Institute of Mental Health, PCP Phencyclidine, pts patients, QoL Quality of life, Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire, RCT randomized controlled trial, RMT resting motor threshold, rTMS repetitive transcranial magnetic stimulation, s second, SADE serious adverse device effect, SCID Structured Clinical Interview for DSM-IV, SD standard deviation, SF 36 PF Short Form (36) Health Survey Physical Functioning, SIGH-SAD Structured Interview Guide for the Hamilton Depression Rating Scale, SNRI serotonin-norepinephrine reuptake inhibitors, SSRI selective serotonin re-uptake inhibitors, TRD treatment-resistant depression, NOS Not Otherwise Specified, MMSE Mini-Mental State Examination, VNS vagus nerve stimulation, vs versus, w week, yrs years

Table A 6: Characteristics of randomised controlled studies comparing rTMS with ECT

Study characteristics						
Author, year, reference number	**Kesthkar, 2011 [19]**	**Eranti, 2007 [18]**	**Rosa, 2006 [54]**	**Grunhaus 2003 [60]**	**Grunhaus 2000, Dannon 2002 [17, 59]**	**Pridmore 2000 [61]**
Study Registration number (Registry identifier)	IRCT138902253930N1	ISRCTN67096930	N/A	N/A	N/A	N/A
Country	Iran	UK	Brazil	Israel	Israel	Australia
Sponsor	Shiraz University of Medical Sciences	NCCHTA, Guy's and St Thomas's Charitable Foundation, National Alliance for Research on Schizophrenia and Depression	N/A	NARSAD	NARSAD	N/A
Comparator	ECT (bilateral)	ECT	ECT	ECT (uni- and bilateral)	ECT	ECT
Study design	RCT	Multicentre RCT	RCT	RCT	RCT	RCT
Number of patients *(I vs C)*	73 (33 vs 40)	46 (24 vs 22)	35 (20 vs 15)	40 (20 vs 20)	40 (20 vs 20)	32 (16 vs 16)
Study duration	N/A	Jan 2002-Aug 2004	N/A	N/A	N/A	N/A
Objectives	To compare the efficacy of rTMS and ECT in TRD patients and the effects on suicidal behaviour.	To test the equivalence of rTMS and ECT.	To compare depression symptoms improvement between rTMS and ECT.	To compare ECT and rTMS for nonpsychotic TRD.	To compare ECT and rTMS for psychotic TRD.	To compare the antidepressant response to rTMS and ECT with treatment courses of unlimited length; to compare the side-effect profiles; to examine the evidence for dose-response relationship.
Model used	Neuro-MS (Neurosoft), figure 8 coil	Magstim Super Rapid Stimulator, figure 8 coil	Magpro, figure 8 coil	Magstim, figure 8 coil	Magstim, figure 8 coil	Magstim, figure 8 coil
Inclusion criteria	MDD according to DSM-IV	Referral by a psychiatrist for ECT, MDD diagnosis by the DSM-IV Axis I Disorders (SCID), right-handedness, >18 yrs	Referral by a psychiatrist for ECT, aged 18-65 yrs, unipolar MDD according to DSM-IV without psychotic symptoms, HAMD-17 ≥22.	Diagnosis of unipolar major depression by DSM-IV, score of at least 18 on Hamilton Depression Rating Scale, 18 years or older, treatment resistant.	> 18 yrs, DSM-IV diagnosis of MDD, ≥ 18 scored on HRSD-17.	TRD, DSM-IV diagnosis of MDD, right-handed, age 25-70, no history of epilepsy.

Study characteristics						
Author, year, reference number	**Kesthkar, 2011 [19]**	**Eranti, 2007 [18]**	**Rosa, 2006 [54]**	**Grunhaus 2003 [60]**	**Grunhaus 2000, Dannon 2002 [17, 59]**	**Pridmore 2000 [61]**
Exclusion criteria	Previous rTMS, implanted device, history of seizure, bipolar disorder, substance abuse, history of significant head trauma, severe medication condition, previous nonresponse to ECT, pregnancy	Metallic implants or foreign bodies, history of seizures, substance misuse in the previous 6 mo, medically unfit for general anaesthesia or ECT, ECT or rTMS in the previous 6 mo, dementia, other axis I diagnosis, inability to provide consent	History of epilepsy, past neurosurgery with metal clips, other neurological or psychiatric diseases, cardiac pacemakers, pregnancy.	Additional Axis I diagnoses, major depression with psychosis, major depression due to medical condition or substance abuse.	Additional Axis I diagnoses, history of seizures, no medical, neurological or neurosurgical disorder that would preclude the administration of rTMS or ECT.	Serious medical illness, intracranial metal objects, mood disorder due to medical condition or substance abuse, co-morbidity for mental disorder.
Add-on or monotherapy	Add-on	Add-on	Mono	Mono (only lorazepam allowed)	Mono (only clonazepam allowed)	Mono
Follow-up duration	N/A	6 mo	N/A	N/A	6 mo	N/A
Loss-to-FU, n (%)	N/A	3 (12) vs 6 (27)	N/A	N/A	2 (4.6)	N/A
Depression scale used	HDRS-24, BDI	HAMD-17	HAMD-17	HRSD-17	HRSD-17	HDRS
Frequency, Hz	N/A	10	10	10	10	20
Trains, n	N/A	20	25	20	20	30-35
Train duration, s	N/A	5	10	6	6	2
Intertrain interval, s	N/A	55	20	30	30	28
Pulses per session	408	1000	2500	1200	1200	N/A
Number of sessions	10 (2 w)	15 (3 w)	20 (4 w)	20 (4 w)	20 (4 w)	Mean 12.2
Total pulses	4080	15000	50000	24000	24000	N/A
Unilateral/bilateral, side if unilateral	Unilateral, left DLPFC	Unilateral, left DLPFC, 5 cm rule	Unilateral, left DLPFC, 5 cm rule	Unilateral, left DLPFC, 5 cm rule	Unilateral, left DLPFC, 5 cm rule	Unilateral, left DLPFC
Intensity of the stimulation (% RMT)	90	110	100	90	90	100
Patient characteristics *(I vs C)*						
Age, y mean (SD)	34.0 (9.9) vs 35.6 (8.1)	63.6 (17.3) vs 68.3 (13.4)	41.8 (10.2) vs 46.0 (10.6)	57.6 (13.7) vs 61.4 (16.6)	58.4 (15.7) vs 63.6 (15.0)	44.0 (11.9) vs 41.5 (12.9)
Sex, male/female, n	13/20 vs 8/32	8/16 vs 6/16	8/12 vs 8/7	6/14 vs 5/15	8/12 vs 6/14	4/12 vs 3/13

Study characteristics						
Author, year, reference number	**Kesthkar, 2011 [19]**	**Eranti, 2007 [18]**	**Rosa, 2006 [54]**	**Grunhaus 2003 [60]**	**Grunhaus 2000, Dannon 2002 [17, 59]**	**Pridmore 2000 [61]**
Previous therapy	≥ 2 trials of antidepressants	Number of antidepressant failed in the current episode 1.7 vs 1.7 SSRI: 6 vs 5 Tricyclics: 2 vs 2 Venlafaxine: 10 vs 7 Mirtazapine: 4 vs 5 Lithium: 5 vs 6 Benzodiazepines: 3 vs 4 Zopiclone: 6 vs 3 Anticonvasculsant mood stabilizers: 2 vs 3 L-Tryptophan: 1 vs 0	≥ 2 trials of antidepressants	≥ 1 course of antidepressant (adequate level for ≥ 4 w)	Previous ECT: 6 vs 9	Previous ECT: 6 vs 3
Depression score at baseline, mean (SD)	BDI: 34.0 (9.6) vs 34.8 (9.9) HDRS: 21.0 (7.5) vs 25.8 (6.1)	BDI: 36.0 (8.7) vs 37.8 (10.5) HAMD: 23.9 (7.0) vs 24.8 (5.0)	30.1 (4.7) vs 32.1 (5.0)	24.4 (3.9) vs 25.5 (5.9)	25.8 (6.1) vs 28.4 (9.3)	HDRS:25.3 (4.1) vs 25.8 (3.6) BDI: 33.9 (6.8) vs 31.8 (6.6)
Suicide score at baseline, mean (SD)	BDI: 1.5 (0.8) vs 1.4 (1.0) HDRS: 1.9 (1.3) vs 2.3 (1.1)	Columbia ECT SSES: 13.2 vs 14.2	N/A	N/A	N/A	N/A
QoL (SF-36, Q-LES-Q) at baseline	N/A	N/A	N/A	N/A	N/A	N/A
Outcomes						
Efficacy *(I vs C)*						
Depression score (at end of treatment, last FU), mean (SD)	BDI: 26.5 (9.2) vs 17.9 (8.3) HDRS: 15.1 (5.6) vs 8.4 (6.1)	*3 w:* HAMD: 18.5 vs 10.7	N/A	13.3 (9.2) vs 13.2 (6.6)	15.4 (7.5) vs 11.2 (8.4)	HDRS: 11.3 (8.5) vs 8.3 (7.5) BDI: 19.2 (11.8) vs 9.6 (8.9)
Response, n (%)	N/A	4 (17) vs 13 (59)	10 (50) vs 6 (40)	11 (55) vs 12 (60)	9 (45) vs 16 (80) *6 mo FU*: 5 vs 12 (4 vs 4 relapsed)	N/A
Remission, n (%)	N/A	4 (17) vs 13 (59) *6 mo FU:* 2/4 (50) vs 6/12 (50)	2 (10) vs 3 (20)	6 (30) vs 6 (30)	N/A	11 (69) vs 11 (69)

Study characteristics						
Author, year, reference number	**Kesthkar, 2011 [19]**	**Eranti, 2007 [18]**	**Rosa, 2006 [54]**	**Grunhaus 2003 [60]**	**Grunhaus 2000, Dannon 2002 [17, 59]**	**Pridmore 2000 [61]**
QoL (SF-36, Q-LES-Q) at end of treatment	N/A	N/A	N/A	N/A	N/A	N/A
Drop-out, n (%)	5 (14) vs 10 (25) due to AEs (2 vs 2), withdrew (3 vs 8)	6 (13) pts discontinued	2 (10) vs 5 (33) (due to 1 hypomania and 1 dissocaitive state in rTMS, 3 suspensions of the ECT treatment and 2 non-attendance in ECT)	N/A	0	N/A
Suicide score post-intervention, mean (SD)	BDI: 1.2 (0.9) vs 0.5 (0.7) HDRS: 1.4 (1.2) vs 0.3 (0.5)	Columbia ECT SSES: 9.7 vs 6.7	N/A	N/A	N/A	N/A
***Safety**, n of pts (%) (I vs C)*						
SADEs						
Seizure	0	N/A	N/A	N/A	0	N/A
Transient cognitive impairment	0	N/A	N/A	N/A	N/A	N/A
Induced current circuits in implanted devices	N/A	N/A	N/A	N/A	N/A	N/A
ADEs						
Headache	1 (3) vs 0	N/A	N/A	3 (15) vs 0	5 (25) vs 0	N/A
Syncope (fainting)	N/A	N/A	N/A	N/A	N/A	N/A
Scalp discomfort	N/A	N/A	N/A	N/A	N/A	N/A
Pain	N/A	N/A	N/A	N/A	N/A	N/A
Facial twitching	N/A	N/A	N/A	N/A	N/A	N/A
Vertigo	N/A	N/A	N/A	N/A	N/A	N/A
Device-related insomnia/drowsiness	N/A	N/A	N/A	2 (10) vs 0	N/A	N/A
Transient induction of hypomania	N/A	N/A	N/A	N/A	N/A	N/A
Mild confusion	N/A	N/A	N/A	N/A	N/A	N/A

Study characteristics						
Author, year, reference number	**Kesthkar, 2011 [19]**	**Eranti, 2007 [18]**	**Rosa, 2006 [54]**	**Grunhaus 2003 [60]**	**Grunhaus 2000, Dannon 2002 [17, 59]**	**Pridmore 2000 [61]**
Transient hearing loss	N/A	N/A	N/A	N/A	N/A	N/A
Other AEs	N/A	N/A	N/A	N/A	N/A	Side-effects rating scores at baseline: 8.1 (3.2) vs 7.9 (1.9) End of treatment: 3.9 (2.9) vs 5.3 (4.3)

Abbreviations: AE adverse event, ADE adverse device effect, BDI Beck Depression Inventory, C control, DLPFC dorsolateral prefrontal cortex, DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, ECT electroconvulsive therapy, FU follow-up, HDRS Hamilton Depression Rating Scale, Hz Hertz, I intervention, major depressive disorder, mo month, n number, N/A not available, NARSAD National Alliance for Research on Schizophrenia and Depression, NCCHTA National Coordinating Centre for Health Technology Assessment, MDD major depressive disorder, pts patients, RMT resting motor threshold, RCT randomized controlled trial, rTMS repetitive transcranial magnetic stimulation, s second, SADE serious adverse device effect, SCID Structured Clinical Interview for DSM-IV, SD standard deviation, SSES suicide severity rating scale, SSRI selective serotonin re-uptake inhibitors, TRD treatment-resistant depression, vs versus, w week, yrs years

List of ongoing and planned studies

Table A7: List of Phase III and IV ongoing studies: sham controlled rTMS trials

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT02213016	September 1, 2016	Interventional	80	rTMS	Sham	MDD	Total scores on the HDRS, Performance on the WCST
JPRN-UMIN000007794	N/A	Interventional	90	a, Navigation-guided HF-rTMS, b, Navigation-guided LF-rTMS	Sham	MDD (monopolar depression)	HDRS-17 and 24, side effects, BDI-II, STAI, neuropsychological testing (VFT, WCST, CST, TMT)
NCT01191333	December 31, 2016	Interventional	164	rTMS	Sham	MDD	Remission (HDRS-17 < 8), response (HDRS-17 diminution > 50%), anxiety (Covi Anxiety Scale), side (UKU side effect rating scale)
NCT02466230	October, 2013	Interventional	28	rTMS	Sham	Depression	Depression Severity measured by HDRS-24, Depression Severity measured by the Public Health Questionnaire-9

Abbreviations: BDI Beck Depression Inventory, CST Color Stroop Test, HDRS Hamilton Depression Scale, HF high-frequency, MDD major depressive disorder, LF low-frequency, rTMS repetitive transcranial magnetic stimulation, STAI State-Trait Anxiety Inventory, TMT Trail Making Test, TRD treatment-resistant depression, VFT Verbal Fluency Test, WCST Wisconsin Card Sorting Test

Sources: clinicaltrials.gov, EudraCT, WHO-ICTRP

We found 13 Phase III and 8 Phase IV studies. From these 21 studies we listed in detail those 4 that are investigating rTMS compared to sham. We found no trials investigating rTMS compared to ECT. Additionally, we found the following categories as presented in the table below.

Table A 8: List of Phase III and IV ongoing studies with rTMS compared to other than sham

Intervention	Comparator	Number of ongoing trials
TMS with EEG	TMS with Near Infrared Spectroscopy (NIRS) Monitoring	1
rTMS + venlafaxine	Venlafaxine alone or sham rTMS	1
Maintenance rTMS	Sham	1
Bilateral theta Burst stimulation	Sham	1
Bilateral rTMS	Monolateral rTMS	1
10 Hz rTMS	Theta Burst stimulation	1
Sinchronized rTMS (NEST-I device)	Sham	1
rTMS + neuronavigation system	rTMS + Standard location system	1
Deep TMS Brainsway H7Coil	H1 Coil as add on therapy	1
Deep HF-TMS	Deep LF-TMS	1
Deep TMS	Sham	1
Deep TMS	HF-rTMS	2
Accelerated rTMS	non-comparative	1
Algorithm guided treatment stratification for MDD	non-comparative	1
Predictive biomarkers of effective treatment with TMS for MDD	non-comparative	2

Abbreviations: EEG electroencephalography, HF high-frequency, LF low-frequency, rTMS repetitive transcranial magnetic stimulation, TMS transcranial magnetic stimulation

Sources: clinicaltrials.gov, EudraCT, WHO-ICTRP

Risk of bias tables

Table A9: Risk of bias – study level (RCTs)

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Medicinal personnel and other staff			
Kang, 2016	Unclear	Unclear	Low	High[8]	Low	Low	Unclear
Chen, 2013	Unclear	Unclear	Low	Unclear[9]	Low	Low	Unclear
Bakim, 2012	Low	Unclear	Low	Unclear	Low	Low	Unclear
Blumberger, 2012	Low	Low	Low	Unclear	Low	Low	Low
Fitzgerald, 2012	Unclear	Unclear	Low	Unclear	High[10]	Low	High

[8] Randomised rater blind study

[9] The sham coil was placed at 90 degrees to the subject's scalp, while the active coil was placed flat on the scalp.

[10] Adverse events not reported.

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Medicinal personnel and other staff			
George, 2010	Low	Unclear	Low	Low	Low	Low	Low
Triggs, 2010	Unclear	Unclear	Low	Low	Low	Low	Unclear
Mogg, 2008	Low	Low	Low	High[11]	Low	Low	Unclear
Bretlau, 2008	Unclear	Unclear	Low	Low	Low	High[12]	High
O'Reardon, 2007	Unclear	Unclear	High[13]	Low	Low	Low	High
Loo, 2007	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Stern, 2007	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Avery, 2006	Low	Unclear	Low	Unclear	Low	Low	Low
Su, 2005	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Holtzheimer, 2004	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Mosimann, 2004	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Fitzgerald, 2003	Low	Low	Low	High[14]	Low	Low	Unclear
Hoppner, 2003	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Boutros, 2002	Low	Unclear	Low	High[15]	Low	Low	Unclear
Garcia-Toro, 2001	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Berman, 2000	Unclear	Unclear	Low	Unclear	Unclear	Low	Unclear
Padberg, 2002	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Loo, 1999	Low	Unclear	Low	Unclear	Low	Low	Unclear
Avery, 1999	Low	Unclear	Low	Unclear	Low	Low	Unclear
Solvason, 2014	Unclear	Unclear	High[13]	Low	Low	Low	High
Keshtkar, 2011	Low	Unclear	High[16]	High[16]	Low	High[5]	High
Eranti, 2007	Low	Low	High[16]	High[16]	Low	Low	High
Rosa, 2006	Low	Unclear	High[16]	High[16]	High[17]	Low	High
Grunhaus, 2003	Low	Unclear	High[16]	High[16]	Low	Low	High
Pridmore, 2000	Unclear	Unclear	High[16]	High[16]	Low	Low	High
Grunhaus, 2000 Dannon, 2002	Low	Unclear	High[16]	High[16]	Low	High[18]	High

[11] Only research physicians knew the type of treatment.

[12] Blinding of outcome assessor unclear.

[13] Patients were instructed not to disclose any treatment details to study raters and they all received the first treatment with the active coil. Therefore the patients might have been able to sport the difference later if they had been allocated to the sham group.

[14] It is stated that the physician administering the treatment was aware of the treatment group.

[15] It is stated in the study that an unblended psychiatrist administered TMS and had minimal interaction with the patients.

[16] Blinding is not possible either for patients or medical staff due to the nature of the intervention.

[17] HDRS scores at T1 and T2 were not reported, only stated that there was a significant difference.

[18] Outcome assessors' blinding unclear.

Table A10: GRADE assessment of rTMS vs sham for TRD

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**rTMS**	**sham**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mean difference in depression scores (assessed with: HDRS)												
16	randomised trials	serious [a,b,c]	not serious	not serious	not serious	none	466	421	not estimable [f]	**MD 2.31** (1.19 to 3.43)	⨁⨁⨁◯ MODERATE	IMPORTANT
Response rate												
19	randomised trials	serious [a,b,c]	serious [d]	not serious	serious [e]	none	144/550 (26.2%)	61/506 (12.1%)	**RR 1.82** (1.18 to 2.82)	**99 more per 1 000** (from 22 more to 219 more)	⨁◯◯◯ VERY LOW	CRITICAL
Remission rate												
12	randomised trials	serious [a,b,c]	not serious	not serious	serious [e]	none	78/449 (17.4%)	28/417 (6.7%)	**RR 2.16** (1.42 to 3.29)	**82 more per 1 000** (from 30 more to 162 more)	⨁⨁◯◯ LOW	CRITICAL
Transient impairment of working memory												
2	randomised trials	serious [a,b,g]	not serious	not serious	very serious [e]	none	5/30 (16.7%)	1/23 (4.3%)	**RR 3.83** (0.48 to 30.59)	**123 more per 1 000** (from 23 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	CRITICAL
Seizures												
11	randomised trials	serious [a,b,g]	not serious	not serious	serious [e]	none	0/341 (0.0%)	0/285 (0.0%)	**RR 0.84** (0.01 to 42.01)	**0 fewer per 1 000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	IMPORTANT

Abbreviations: CI: Confidence interval; **RR:** Risk ratio, **MD**: mean difference

[a] The blinding of medical personnel was unclear in many studies and in some studies the personnel who administered the intervention was aware of the treatment type (if active or sham).
[b] Many studies did not report details about randomization (sequence generation, allocation concealment)
[c] ITT principle was not always adequately realized.
[d] The degree of heterogeneity among studies was moderate (I-square=50%, p<.0001))
[e] The number of events is lower than 300.
[f] Continuous outcome
[g] The studies were not designed to find differences in safety outcomes (the power of the studies is calculated for efficacy outcomes)

Sources: [13, 14]

Table A 11: GRADE assessment of rTMS vs ECT for TRD

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ECT**	**rTMS**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mean difference in depression scores (assessed with: HDRS/HAMD)												
4	randomised trials	serious [a,b,c]	serious [d]	not serious	serious [e]	none	96	89	not estimable[k]	**MD -5.97** (-11.00 to -0.94)	⨁◯◯◯ VERY LOW	IMPORTANT
Response rate												
3	randomised trials	serious [a,f]	serious [g]	not serious	serious [h]	none	41/62 (66.1%)	24/64 (37.5%)	**RR 1.72** (0.95 to 3.11)	**270 more per 1 000** (from 19 fewer to 791 more)	⨁◯◯◯ VERY LOW	CRITICAL
Remission rate												
3	randomised trials	serious [a]	serious [i]	not serious	serious [h]	none	30/58 (51.7%)	21/60 (35.0%)	**RR 1.44** (0.64 to 3.23)	**154 more per 1 000** (from 126 fewer to 781 more)	⨁◯◯◯ VERY LOW	CRITICAL
Transient impairment of working memory												
1	randomised trials	serious [a,b,c,j]	not serious	not serious	serious [e,h]	none	0/40 (0.0%)	0/33 (0.0%)	**RR 1.13** (0.02 to 55.96)	**0 fewer per 1 000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Seizures												
2	randomised trials	serious [a,b,f,j]	not serious	not serious	serious [e,h]	none	0/60 (0.0%)	1/53 (1.9%)	**RR 3.39** (0.14 to 81.46)	**45 more per 1 000** (from 16 fewer to 1,000 more)	⨁⨁◯◯ LOW	IMPORTANT

Abbreviations: CI: Confidence interval; **RR:** Risk ratio

[a] Blinding is not possible because of the nature of the intervention.
[b] The studies did not report details about allocation concealment.
[c] Some studies were unclear about the assessors' blinding.
[d] There was a high degree of heterogeneity among studies (I-squre=70.6%, p=.017)
[e] Small number of patients.
[f] One study was unclear about assessors' blinding.
[g] There was a high degree of heterogeneity among studies (I-square=60.6%, p=.079)
[h] Small number of events.
[i] There was a high degree of heterogeneity among studies (I-square=69.1%, p=.039)
[j] The studies were not designed to find differences in safety outcomes (the power of the studies is calculated for efficacy outcomes)
[k] Continuous outcome

Source: [13]

Applicability tables

Table A12: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The general characteristics of the enrolled patients were homogeneous including the mean age, sex and depression score at baseline. There was heterogeneity in how the studies defined treatment-resistance (ranging from failure of one antidepressant treatment to failure of two antidepressants or even failure of an ECT therapy). Some studies excluded patients who already had ECT treatment. Interpretation of the data is hindered by the non-unified TRD definitions. The number of failed treatments might have an effect on the effectiveness of the technology, therefore it would be necessary to consider a uniform definition for TRD and apply it consistently in the clinical trials.
Intervention	The clinical studies conducted with rTMS do not always reflect the intended clinical use of the device. If it is intended to be used as monotherapy, the study protocol should allow only the use as monotherapy and not as add-on therapy and the treatment parameters should also be carefully defined and unified across studies.
Comparators	We considered sham and ECT as comparators in our assessment. As there is no standard treatment algorithm available, we chose the comparator based on what is currently the most effective treatment to achieve response for very severe depression that has not responded to any other treatment. Although, as it is suggested by CANMAT [6], rTMS response rates are poor in patients where ECT has failed, indicating that rTMS should rather be considered prior to ECT and patients who have not responded to ECT are unlikely to respond to rTMS. rTMS and ECT differ in their mechanisms, tolerability, and acceptability by patients and may be best considered as complementary rather than competing techniques. TMS may be an option in the early stages (stage 1 or 2) after one or two antidepressant therapies have failed. The place in the treatment hierarchy could precede more invasive interventions such as ECT, VNS and DBS, after failure to respond to 4 or more adequate antidepressant treatments [8, 25].
Outcomes	Change in depression scores, remission and response rates were the primary outcomes assessed and also these were the ones most frequently reported on. The time period for reporting the data was typically for the duration of the study (2-6 weeks), with some follow-up studies of 3-6 months. Ideally, outcomes such as quality of life and function would be primary outcomes that determine the impact of the intervention, but this was not reported in the included studies, except for one. A major limitation in the outcomes is that they are not measuring directly the improvement in the patients' quality of life and that there is short-term data available. Due to the lack of long-term data it is not possible to draw conclusion about the long-term effect and safety of the intervention. Some studies reported relapse, but we have no information how the treatment impacted patients' lives in terms of daily functioning, returning to work etc.
Setting	The majority of the included studies were conducted in the USA, Australia, Canada, and Israel; some in Germany, Iran, UK, Taiwan, Spain, Denmark and Turkey. There is no reason to suspect that the etiology of MDD and TRD are substantially different in other European countries. The clinical setting used in the studies reflects the setting in which the intervention will be typically used.

Abbreviations: CANMAT Canadian Network for Mood and Anxiety Treatments, DBS deep brain stimulation, ECT electroconvulsive therapy, MDD major depressive disorder, rTMS repetitive transcranial magnetic stimulation, UK United Kingdom, TRD treatment-resistant depression, VNS vagus nerve stimulation

Sources: Health Quality Ontario [13], CANMAT [6], RAZCP [25], CME [8]

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table A13: Regulatory status

Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
Neurostar TMS Therapy® System							
Europe	Notified Body	Yes	NeuroStar TMS Therapy is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode	NeuroStar TMS Therapy should not be used with patients who have non-removable conductive metal in or near the head. NeuroStar TMS Therapy has not been studied in patients who have not received prior antidepressant treatment.	2012	Yes	N/A
USA	FDA	Yes	NeuroStar TMS Therapy is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode	NeuroStar TMS Therapy should not be used with patients who have non-removable conductive metal in or near the head. NeuroStar TMS Therapy has not been studied in patients who have not received prior antidepressant treatment.	2008	Yes	K083538
Australia	TGA	Yes	NeuroStar TMS Therapy is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode	N/A	2015	Yes	N/A
Mag&More: PowerMAG							
Europe	Notified Body	Yes	Treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode	• patients with metal implants in the head area, e.g. shunts, clips (for patients with metallic implants or similar objects in the vicinity of the point of treatment, the user must weigh the potential risk against the utility of the treatment), • patients with implanted medical devices (cochlear implant, medication pump, pacemaker, etc.), • during pregnancy (in this case the magnetic nerve root stimulation is of critical importance; the transcranial stimulation is less critical on the basis of the greater distance to the foetus), • patients with increased intracranial pressure (e.g. after trauma or infection),	N/A	Yes	N/A

Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
				• patients with a history of epileptic seizures (only applies for the cortical use; if necessary a risk/benefit analysis should be performed), • increased cerebral susceptibility to epileptic seizures through medication (e.g. wellbutrin, zoloft, adderall, fluoxetine, aripiprazole, lithium carbonate, clonazepam)			
USA	FDA	No	N/A	N/A	N/A	N/A	N/A
Magstim: Rapid2 Therapy System, Super Rapid2							
Europe	Notified Body	Yes	rTMS is indicated for patients that have not responded to pharmaceutical solutions – it is estimated that up to 40% of patients do not benefit from, or cannot tolerate, anti-depressant medications – even after repeated attempts.	N/A	N/A	Yes	N/A
USA	FDA	Yes	The Rapid2 and Super Rapid2 Therapy Systems are indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from prior antidepressant medication in the current episode.	N/A	2015	Yes	K143531
Neurosoft: Neuro-MS, Neuro-MS/D							
Europe	Notified Body 0535	Neuro-MS: Yes Neuro-MS/D: Yes	N/A	N/A	Neuro-MS: 2015 Neuro-MS/D: 2009	Neuro-MS: Yes Neuro-MS/D: Yes	Neuro-MS: CE577342 Neuro-MS/D: N/A
USA	FDA	Neuro-MS/D: Yes	N/A	N/A	2016	Yes	K160309
Australia	TGA	Neuro-MS/D: Yes	N/A	N/A	2016	Yes	DV-2015-MC-06490-1

Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch	Approval number (if available)
Magventure: MagVita TMS Therapy System							
Europe	Notified Body	Yes	MagVita TMS Therapy™ is approved for the treatment of MDD in adult patients who have failed to achieve satisfactory improvement from two prior antidepressant medications, at or above the minimal effective dose and duration in the current episode.	N/A	N/A	Yes	N/A
USA	FDA	Yes	The MagVita TMS Therapy System is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode.	N/A	2015	Yes	K150641

Abbreviations: CE Conformité Européene, FDA Food and Drug Administration, MDD major depressive disorder, N/A not available, TGA Therapeutic Goods Administration, TMS transcranial magnetic stimulation

Sources: [34, 36, 40, 104-109]

Table A14: Summary of reimbursement recommendations in European countries for the technology

Country and issuing organisation e.g. G-BA, NICE	Summary of reimbursement recommendations and restrictions	Summary of reasons for recommendations, rejections and restrictions
Germany, G-BA	In Germany, no HTA report, guidance document, or reimbursement decision on rTMS for depression has been published so far. In ambulatory care, rTMS is not reimbursed by statutory sickness funds. However, some private insurance companies pay for rTMS in treatment-resistant depression.	In 2015, DGPPN issued multi-disciplinary, evidence-based guidelines on the treatment of depression [22]. According to these guidelines, rTMS should be considered only as a therapeutic option. This statement is limited to high-frequency rTMS of the left dorsolateral prefrontal cortex in patients with symptoms despite drug therapy.
UK, NICE	Recommended as an option within normal arrangements for audit, the device used with the procedure is a local decision.	The evidence on repetitive transcranial magnetic stimulation for depression shows no major safety concerns. The evidence on its efficacy in the short‑term is adequate, although the clinical response is variable [23].
France, HAS	The Department for the Evaluation of Medical Procedures at HAS has not evaluated this technique; however a request had previously been submitted by a professional organisation.	It is not currently reimbursed if done outside of the hospital. The technique is reimbursed/ covered if carried out in the course of a hospitalization (a patient hospitalized for depression).
Poland, AOTMiT	The technology is not reimbursed in Poland. No HTA assessment has been conducted.	It may be used and financed by DRG groups.
Portugal, INFARMED	The technology is not reimbursed in Portugal. No HTA assessment has been conducted.	It is possible for each hospital to proceed with its direct acquisition.
Slovenia, NIJZ	The technology is not reimbursed in Slovenia. No HTA assessment has been conducted.	The technology is used for other indications in Slovenia.
Spain, RedAETS	This technology is not explicitly included in the Spanish Portfolio of the National Health Service.	There is a low degree of adoption by some private health institutions in the country.
Hungary, OGYEI	The technology is not reimbursed in Hungary.	No HTA assessment has been conducted.
Netherlands	The technology is not reimbursed.	No HTA assessment has been conducted.
Croatia, CHIF	Mapping, initial assessment and examination, and max. 30 therapy sessions are reimbursed, for use only in health institutions. Indication: Depression – moderate and severe episodes Stimulation of left DLPFC (20 Hz; 2 sec train, 40 pulses, pause 28sec; 40 repetitions = 1,600 pulses). Stimulation of right DLPFC (1 Hz – excitation; 1,600 sec; 1 repetition). 20 -30 min per treatment, 2 -4 weeks (10-20 treatments) are recommended, can be delivered in combination with psychotherapy. Exacerbations – maintenance therapy.	Guidelines for therapy are cited in: Perera et al. The Clinical TMS Society Consensus Review and Treatment Recommendations for TMS Therapy for Major Depressive Disorder [42].
Italy, Reg. Emilia-Romagna	The technology is not reimbursed.	No HTA assessment has been conducted.
Belgium, KCE	The technology is not reimbursed.	No HTA assessment has been conducted.

Abbreviations: G-BA Gemeinsamer Bundesausschuss, NICE National Institute for Health and Care Excellence, AOTMiT Agencja Oceny Technologii Medycznych i Taryfikacji/Agency for Health Technology Assessment and pricing, NIJZ National Institute of Public Health Slovenia, INFARMED National Authority of Medicines and Health Products, HAS French National Authority for Health, DRG diagnosis-related group, CHIF Croatian Health Insurance Fund, OGYEI Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet/National Institute of Pharmacy and Health Products, RedAETS Red Española de Agencias de Evaluación de Tecnologías Sanitarias, rTMS repetitive transcranial magnetic stimulation, DGPPN Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde/ German Association for Psychiatry, Psychotherapy, and Psychosomatics, DLPFC dorsolateral prefrontal cortex, HTA health technology assessment

Sources: [22, 23, 42]

Table A15: Summary of recommendations in European countries for the technology in the indication under assessment

Country	Organisation	Summary of recommendations and restrictions	Summary of reasons for recommendations and restrictions
UK	NICE	Recommended as an option within normal arrangements for audit, the device used with the procedure is a local decision.	The evidence on repetitive transcranial magnetic stimulation for depression shows no major safety concerns. The evidence on its efficacy in the short-term is adequate, although the clinical response is variable [23].
Germany	DGPPN	rTMS should be considered only as a therapeutic option.	The level of recommendation for the use of HF-rTMS to the left DLPFC is A [22].
Spain	AVALIA-t	rTMS as an add-on therapy is currently not recommended.	There is uncertainty in its clinical efficacy [81].
Spain	SESCS	rTMS is recommended for TRD when there are no other alternatives of proven therapeutic value.	The decision to apply rTMS or ECT should be discussed with the patient in a shared decision making framework in which the risk-benefit balance of the options are discussed. Regarding the effectiveness of rTMS, statistically significant effects were obtained. However, except for the overall effect of the technique on the short-term reduction of depressive symptoms, the evidence is insufficient to establish its efficacy in the treatment of TRD because it comes from studies with small samples that yield imprecise estimations [110].

Abbreviations: AVALIA-t Galician Agency for Health Technology Assessment, NICE National Institute for Health and Care Excellence, DGPPN Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde/ German Association for Psychiatry, Psychotherapy, and Psychosomatics, DLPFC dorsolateral prefrontal cortex, rTMS repetitive transcranial magnetic stimulation, HF high-frequency, SESCS Evaluation Unit of the Canary Islands Health Service

Sources: [22, 23, 81, 110]

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1	**Ethical**	
1.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	**Yes**/No
	rTMS is indicated for those patients with major depressive disorder who remain disabled despite the use of antidepressants or because of their inability to tolerate medication side effects. By definition the TRD does not include non-willingness to undergo ECT treatment or non-tolerance of ECT. Nevertheless, if rTMS could not be used, those who are unable to tolerate or refuse ECT would be left without any treatment option.	
1.2	Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	**Yes**/No
	There is little knowledge about the exact patient group that could benefit the most from the new technology, but there might be a group where the efficacy and safety undoubtedly favours rTMS. Special populations like the elderly or adolescent patients could benefit from the use of the technology and would opt for the technology rather than ECT in the treatment algorithm. Treatment resistance is more frequent in the elderly and the risk of drug interactions is especially high. rTMS is free of the side effects of antidepressant drugs, is physically less demanding than ECT, and it is not subject to drug interactions. However, these patient populations were out of scope of this assessment and currently there is little research on the efficacy and safety of rTMS in them [111].	
2	**Organisational**	
2.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	**Yes**/No
	rTMS requires a physician with specialised knowledge, a silent room where the patient can lie down and the stimulator can be applied. Personnel skilled in the management of syncope and seizure are required. The technology is relatively staff intensive.	
2.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	**Yes**/No
	The new technology does not require anaesthesia. Nevertheless, the patients need to go to the hospital 5 times a week for at least 2 weeks and get the treatment, which requires free capacities at the hospital in terms of personnel and space.	
3	**Social**	
3.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	**Yes**/No
	The use of the comparator technology, ECT may lead to stigmatisation.	
3.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	**Yes**/No
	The comparator, ECT, is associated with stigmatization. Repetitive TMS does not have this property.	
4	**Legal**	
4.1	Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	Yes/**No**
4.2	Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	Yes/**No**

APPENDIX 4: DIAGNOSTIC CRITERIA ACCORDING TO DSM-IV-TR

Major Depressive Disorder Diagnostic Criteria according to DSM-IV-TR

A	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is (1) depressed mood or (2) loss of interest or pleasure. (1) Depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others. (2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day. (3) Significant weight loss when not dieting or significant gain, or decrease or increase in appetite nearly every day. (4) Insomnia or hypersomnia nearly every day. (5) Psychomotor agitation or retardation nearly every day. (6) Fatigue or loss of energy nearly every day. (7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). (8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). (9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide.
B	The symptoms do not meet the criteria for a mixed episode
C	The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
D	The symptoms are not due to the direct physiological effects of a substance (for example, a drug of abuse, a medication), or a general medical condition (for example, hyperthyroidism).
E	The symptoms are not better accounted for by bereavement, i.e. after the loss of a loved one, the symptoms persist for longer than 2 months or are characterised by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms or psychomotor retardation.
Source: American Psychiatric Association. DSM-IV-TR. Diagnostic and statistical manual of mental disorders, 4th ed. Barcelona: Masson 2003.	

Source: APA [112]

APPENDIX 5: SAFETY GUIDELINES

Table A3: Maximum Safe Duration of Single Trains Repetitive Transcranial Magnetic Stimulation

Frequency (Hz)	Stimulus Intensity (% of Motor Threshold)[a]				
	90%	100%	110%	120%	130%
1	> 1,800	> 1,800	> 1,800	> 360	> 50
5	> 10	> 10	> 10	> 10	> 10
10	> 5	> 5	> 5	4.2	2.9
20	2.05	2.05	1.6	1.0	0.55
25	1.28	1.28	0.84	0.4	0.24

[a]Numbers preceded by > are the longest duration tested.
Data from Wassermann[10] Reprinted from Clinical Neurophysiology, *120/12, Rossi et al, Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research, 2008–39, 2009, with permission from Elsevier.[9]*

Table A4: Updated Recommendations: Maximum Safe Duration of Pulses for Individual Trains at Each Stimulus Intensity

Frequency (Hz)	Stimulus Intensity (% of Motor Threshold)							
	100%		110%		120%		130%	
	Duration[a]	Pulses	Duration[a]	Pulses	Duration[a]	Pulses	Duration[a]	Pulses
1	> 270	> 270	> 270	> 270	> 180	> 180	50	50
5	10	50	10	50	10	50	10	50
10	5	50	5	50	3.2	32	2.2	22
20	1.5	30	1.2	24	0.8	16	0.4	8
25	1.0	25	0.7	17	0.3	7	0.2	5

[a]Dur ond.
Reprinted from Clinical Neurophysiology, *120/12, Rossi et al, Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research, 2008–39, 2009, with permission from Elsevier.[9]*

Table A5: Safety Recommendations for Safe Inter-Train Interval for 10 Trains at < 20 Hz

Inter-train Interval (ms)	Stimulus Intensity (% of Motor Threshold)			
	100%	105%	110%	120%
5,000	Safe	Safe	Safe	Insufficient data
1,000	Unsafe (EMG spread after 3 trains)	Unsafe[a]	Unsafe (EMG spread after 2 trains)	Unsafe (EMG spread after 2 trains)
250	Unsafe[a]	Unsafe[a]	Unsafe (EMG spread after 2 trains)	Unsafe (EMG spread after 3 trains)

Abbreviation: EMG, electromyographic.
[a]These stimulus parameters are considered unsafe because adverse events occurred with stimulation of lower intensity or longer inter-train interval, but no adverse effects were observed with these parameters.
Reprinted from Clinical Neurophysiology, *120/12, Rossi et al, Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research, 2008–39, 2009, with permission from Elsevier.[9]*

Source: HQO [13]

An appendix with comments from external experts, as well as responses from authors, for the purposes of transparency, can be found separately.