Repetitive transcranial magnetic stimulation for treatment-resistant major depression

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

Ludwig Boltzmann Institut
Health Technology Assessment

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Project Team

Project leader: Dr. Katharina Hawlik, MSc

Authors: Judit Erdös, MA
Nora Ibargoyen Roteta, MSc, PhD
Iñaki Gutiérrez Ibarluzea

Project Support

Systematic literature search: Tarquin Mittermayr, BA

External Review: 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. Dr. Jose Mª Vergara Ugarriza, Head of Neurophysiology of Miguel Servet University Hospital (Zaragoza), Aragon

Internal Review: Lilisbeth Perestelo Perez, MPsych, PhD
Amado Rivero-Santana
Nancy Thiry, MSc
Dr. Katharina Hawlik, MSc

Proof reading: Michal Stanak, MA

Factual accuracy check: Neurosoft, Russia
Mag&More GmbH, Germany

Correspondence

Judit Erdös, MA. judit.erdos@hta.lbg.ac.at

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Conflict of interest

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

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the LBI-HTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the LBI-HTA.

The HTA Core Model®, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. The following version of the Model was used: HTA Core Model Application for Rapid Relative Effectiveness (REA) Assessments (4.2). Use of the HTA Core Model does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

CONTENT INFORMATION

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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
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

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).

aim

Introduction

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) [1] (A0002).

target population: patients with TRD

The prevalence of unipolar TRD is not clear due to the lack of internationally acknowledged and standardized definition. However, there are reasonable estimates available. 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% [5, 6, 44] (A0023).

unclear prevalence

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 [1] (A0024).

diagnosis: DSM-IV-TR criteria

Description of technology and comparators

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neurostimulation and neuromodulation technique, which 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 [5, 7], 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 [7, 8].

rTMS: non-invasive neurostimulation
Technical parameters:
- frequency
- intensity
- train duration
- intertrain interval
- number of trains per session
- number of pulses per session

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 and train duration of 4 s with intertrain interval of 26 s [9]. However, the stimulation parameters required to optimize the efficacy of rTMS treatment are not well known.

contraindications

The use of the rTMS is prohibited for patients with metal implants in the head area, implanted medical devices during pregnancy, increased intracranial pressure, a history of epileptic seizures, increased cerebral susceptibility to epileptic seizures through medication and unstable general medical disorders [7, 8, 10] (A0001).

benefits: non-invasive, no cognitive side-effects, no general anaesthesia needed, no post-session recovery needed

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, hence the patient can resume normal activities immediately and no cognitive side-effects have been reported with rTMS.

Comparators

comparators: sham stimulation (with a sham coil) …

Sham stimulation is delivered with a sham coil.

… and ECT (neuromodulation under general anaesthesia, induction of a seizure to the brain)

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 [11]. 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 [12]. As regards to mortality, ECT is a safe procedure with a very low mortality rate (1 death per 73,440 treatments) [11] (A0001). However, cognitive effects including transient disorientation when recovering from ECT sessions, retrograde and anterograde amnesia, mild, short-term impairment in memory and other cognitive domains during and after treatment with ECT might occur. [4, 11] (B0002).

Methods

2-step systematic literature search:
1. SRs and HTAs
2. RCTs

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. The AMSTAR tool was used for quality assessment of SRs, and as a result, the Health Quality Ontario (HQO) report [13] was selected for update.

HQO report selected for update
Inclusion of additional 2 RCTs

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 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 the quality of RCTs. For the assessment of the strength of evidence, the Grading of Recommendations, Assessment, Development and Evaluation approach was used.

Cochrane risk of bias tool to assess quality
GRADE approach to assess the strength of evidence

Clinical effectiveness

critical endpoints: response and remission

The critical endpoints in assessing clinical effectiveness were response and remission rates. The mean difference in depression scores was considered important, but not critical endpoint.

Safety

The critical endpoint in assessing safety was cognitive impairment, whereas the number of seizures was considered important endpoint.

critical endpoint: cognitive impairment

Results

Available evidence

rTMS vs sham

23 studies met the inclusion criteria in the HQO report. We found two additional RCTs [14, 15] that are included in the present analysis. One of them [15] is the 6 month follow-up of a study included in the HQO report [16]. A total of 1180 patients were analysed in the studies, 615 in the rTMS arm and 565 in the sham arm.

25 included studies with 1180 patients

The inclusion criteria of the studies varied as follows:

inclusion criteria

- 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 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.

varying stimulation parameters

rTMS vs ECT

The HQO report 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 [17, 18].

6 included studies with 266 patients

The inclusion criteria of the studies varied as follows:

inclusion criteria

- 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
  - In 1 study only the number of failed antidepressants in the current episode was reported

- rTMS as add-on or monotherapy
  - In 2 studies: add-on therapy
  - In 2 studies: monotherapy
  - In 2 studies: only lorazepam or clonazepam were allowed

varying stimulation parameters

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 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 a figure 8 coil.

Clinical effectiveness

rTMS vs sham

RR for response: 1.82 favouring rTMS

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.

RR for remission: 2.16 favouring rTMS

The pooled risk ratio for remission rate across 12 studies 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).

MD 2.31 points favouring rTMS

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 clinically important (threshold of 3.5 points).

significant improvement favouring rTMS in general health, mental health, and Q-LES-Q

There was a statistically significant improvement favouring rTMS on the general health and mental health SF-36 subscales at 4- and 6-week follow-up. Statistically significant improvement favouring rTMS was also seen in the Q-LES-Q total score at 4-and 6-week follow-up [15] (D0012, D0013).

rTMS vs ECT

RR for response: 1.72 favouring ECT, but statistically not significant

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 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 (D0006).

RR for remission: 1.44 favouring ECT, but statistically not significant

The pooled risk ratio for remission 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).

MD 5.97 points favouring ECT

The weighted mean difference of depression scores from baseline to the end of treatment was -5.97 points (95% CI -11.00 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 (I2=72.2%, p=.013) (D0005).

decrease in suicide scores greater in the ECT group

One study [19] 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

most common side-effect: headache

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 from 0 to 50% in the sham group. Seizures did not occur in any of the studies and 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 adverse events

No serious safety concerns were identified. The most common side-effect was headache in rTMS-treated patients. No adverse events occurred in ECT-treated patients (C0008).

Upcoming evidence

4 ongoing studies rTMS vs sham

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

Reimbursement

currently not reimbursed

The technology is not reimbursed in the majority of the 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.

Discussion

very low quality of the body of evidence

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

methodological limitations

The methodological limitations of the studies included in this assessment are likely to influence the 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).

QoL outcomes and patient satisfaction neglected in the studies

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

rTMS is safe and well-tolerated, more effective than sham, unclear effectiveness compared to ECT

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. It remains unresolved if rTMS is as effective as ECT, since no significant differences in remission and response rates where 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.

further research needed

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

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Fragestellung

Der Fokus dieses Berichts liegt in der Bewertung der transkraniellen Magnetstimulation zur Behandlung therapieresistenter Depression (TRD). Der Bericht ging der Frage nach, ob repetitive transkranielle Magnetstimulation (rTMS) im Vergleich zu einer Scheinintervention und im Vergleich zur Standardintervention der Elektrokonvulsionstherapie gleich wirksam bzw. wirksamer und gleich sicher, bzw. sicherer ist bei der Behandlung der TRD.

Definition TRD: schwere Depression, keine Verbesserung durch verschiedene AD Therapie

Unter TRD wird eine schwere Form der Depression verstanden (im Englischen *Major Depression Disorder*, MDD), bei nach mindestens zwei Versuchen verschiedener Antidepressiver Therapie (AD) sich keine Verbesserung einstellt. Eine allgemeingültige Definition gibt es zurzeit jedoch noch nicht. Die genaue Definition ab wann eine schwere Depression therapieresistent ist, ist auch deshalb schwierig, da es keine Einigung gibt was als Therapieansprechen gilt. In vielen Studien wird Therapieansprechen als eine mehr als 50 prozentige Verbesserung auf der Depression Skala eingestuft [1].

MDD = schwere Depression, nach DSM-IV TR diagnostiziert

MDD wird derzeit mit den *Diagnostic Criteria for Major Depressive Disorder and Depressive Episods* (DSM-IV-TR) diagnostiziert (Details in Appendix 4). Alternative Verdachtsdiagnosen, wie bipolare Depression oder dysthymische Störung, sollten aufgrund der unterschiedlichen Behandlungsmöglichkeiten ausgeschlossen werden. Therapieresistente PatientInnen werden durch Anamnese und Krankengeschichte identifiziert.

Prävalenz: nicht klar, geschätzt: bis zu 50 % der PatientInnen kein Therapieansprechen auf AD-Therapie

in Österreich: 140.000 PatientInnen mit Depression, circa 15 % TRD

Die Prävalenz der unipolaren TRD ist aufgrund der fehlenden international anerkannter Definition nicht klar. Schätzungen zufolge sprechen 30-40 % oder 50 % der PatientInnen – abhängig von der gewählten Definition des Therapieansprechens – nicht auf eine AD-Therapie an [3, 5, 44]. In Österreich werden 120.000 bis 140.000 Patienten pro Jahr mit Depressionen diagnostiziert, von denen nur 24.000 bis 36.000 ausreichend behandelt und Remission erreicht wird [48]. Von den restlichen 84.000 bis 116.000 Patienten, werden geschätzte 10-15 % (8.400 bis 17.400 Personen) nicht auf eine Therapie ansprechen.

Beschreibung der Technologie

rTMS: nicht-invasive kranielle Stimulation

verschiedene Arten und Intensitäten (niedrig und hochfrequent rTMS)

Die repetitive transkranielle magnetische Stimulation (rTMS) ist eine nichtinvasive Neurostimulation, die als eine Reihe Einzelimpulsen über eine Magnetspule auf den Kortex übertragen wird. Die typischsten technischen Daten eines Einzelstimulus sind die Frequenzen (Hochfrequenz-Stimulation >1Hz [5, 7] oder Niederfrequenz-Stimulation bei ≤ 1 Hz), Intensität, Stimulationsdauer, Intervall zwischen den einzelnen Stimuli, und die Anzahl der Stimuli pro Sitzung [7, 8].

unterschiedliche Behandlungsprotokolle, meist: FDA-Standardparameter

Es gibt verschiedene Behandlungsprotokolle, wobei die FDA-basierten Standardparameter am weitesten verbreitet sind und für diesen Bericht berücksichtigt wurden: 10 magnetische Impulse pro Sekunde (Hz), 3.000 Impulse pro Sitzung, 100 bis 120 % Intensität, Stimulationsdauer von 4 s mit stimulationsfreiem Intervall von 26 s [9]. Die optimalen Einstellungen für die Wirksamkeit der rTMS sind allerdings nicht belegt.

rTMS indiziert für PatientInnen mit MDD ohne Verbesserung bei AD Therapie

rTMS: wenig invasiv, ambulant, keine kognitiven Einschränkungen nach Behandlung

rTMS ist für PatientInnen mit unipolarer, schwerer Depression (MDD) indiziert, die keine zufriedenstellende Verbesserung durch vorangegangene AD Therapie hatten. Der erwartete Vorteil der rTMS gegenüber der Vergleich Intervention der elektrokonvulsiven Therapie (ECT) ist die geringe Invasivität, die ambulante Anwendung ohne Notwendigkeit einer Anästhesie und Aufwachphase. Die PatientInnen können ihrer Tätigkeit im Anschluss der Intervention ohne Einschränkungen nachgehen. Es wurden des Weiteren keine kognitiven Einschränkungen bei der Behandlung mit rTMS berichtet. Bei ECT Sitzungen hingegen, können vorübergehende kognitive Einschränkungen vorkommen, und umfassen Desorientierung beim Aufwachen, Amnesie, Beeinträchtigung des Gedächtnisses während und nach der Behandlung mit ECT. Allerdings sind diese Nebenwirkungen üblicherweise nur vorübergehend mit Wiederherstellung der vollen kognitiven Funktionen innerhalb von Wochen oder Monaten [4, 11].

diverse Kontraindikationen

Kontraindikationen für die Anwendung von rTMS sind PatientInnen mit Metallimplantaten im Kopfbereich, implantierte Medizinprodukte (Cochlea-Implantat, Herzschrittmacher, etc.), Schwangerschaft, erhöhter intrakranieller Druck, Epilepsie bzw. erhöhte zerebrale Anfälligkeit für epileptische Anfälle und allgemeine instabile Komorbiditäten [7, 8, 10].

Methoden

Zur Beantwortung der Forschungsfrage wurde eine systematische Literatursuche und -analyse in zwei Phasen durchgeführt: als erster Schritt wurden Sekundärstudien (z. B. HTA-Berichte und systematische Reviews/SRs) anhand ihrer Qualität, und ihrer Einschluss- und Ausschlusskriterien bewertet. Zur Qualitätsbewertung der SRs wurde AMSTAR-Tool verwendet. Aus insgesamt 20 vorliegenden SR wurde der Health Quality Ontario (HQO Bericht) [13] ausgewählt. In einem zweiten Schritt wurde eine ergänzende Suche nach Primärstudien durchgeführt, die seit der Literatursuche des gewählten HQO-Berichts [13] veröffentlicht wurden, und führte zum Einschluss zweier randomisierter, kontrollierter Studien (RCT) [14, 15]. Die Studien verglichen HF-rTMS mit der linken DLPFC mit einer Scheinintervention. Es wurden keine weiteren Primärstudien gefunden, die rTMS mit ECT verglichen haben.

Klinische Wirksamkeit

entscheidende Endpunkte Wirksamkeit

Die Endpunkte Therapieansprechrate und Remissionsrate wurden für die Beurteilung der Wirksamkeit als entscheidend definiert. Des Weiteren wurde eine durchschnittliche Verbesserung auf der Depressionsskala (HDRS) als wichtiger, jedoch nicht entscheidender Endpunkt herangezogen.

Sicherheit

entscheidende Entpunkte Sicherheit

Der entscheidende Endpunkt für die Beurteilung der Sicherheit war die kognitive Einschränkung; wobei die Anzahl der Anfälle als wichtiger Endpunkt eingestuft wurde.

Ergebnisse

Verfügbare Evidenz

rTMS vs sham

verfügbare Evidenz: SR mit 23 Studien, 2 RCTs

Im HQO Bericht erfüllten 23 Studien die Einschlusskriterien, die durch zwei zusätzliche RCTs aus der Primär Suche ergänzt wurden [14, 15]. Eines der beiden RCTs [15] ist eine 6-Monats-Follow-up Studie einer im HQO-Bericht bereits enthaltenen Studie [16]. Insgesamt wurden 1.180 Patienten in den Studien analysiert, 615 im aktiven rTMS-Arm und 565 im Scheinarm.

unterschiedliche Einschlusskriterien der verschiedenen Studien in Bezug auf Ausgangswerte, AD-Einnahme und Stimulationsparameter

Die Einschlusskriterien der Studien unterschieden sich folgendermaßen:

- Ausgangwerte auf der HDRS-17 Skala:
  - 11 Studien: >25 HDRS-17 (schwere Depression)
  - 14 Studien: 19 bis 24 (moderate Depression)
- AD- Einnahme:
  - 16 Studien: vorangegangener AD-Therapieversuch mit zwei oder mehr AD
  - 9 Studien: vorangegangener AD-Therapieversuch mit einem oder mehr AD
  - 17 Studien: rTMS unter AD- Therapie
  - 8 Studien: keine AD Therapie während rTMS
- Stimulationsparameter:
  - Frequenz (5 bis 20 Hz), Intensität (80 bis 120 %), Anzahl der Stimulationen pro Sitzung (15 bis 75), die Stimulationsdauer (2 bis 10 Sekunden), Zwischenintervall (22 bis 58 Sekunden), Anzahl der Impulse pro Sitzung von (800 bis 3.000) Gesamtzahl der Impulse während der rTMS-Behandlung (8.000 bis 90.000).
  - Alle Studien verwendeten die *Figur 8* Spulen.

rTMS vs ECT

verfügbare Evidenz: SR mit 6 Studien, 266 PatientInnen, 133 pro Arm

Der HQO-Bericht enthielt sechs Studien, die rTMS mit ECT verglichen. Die meisten Studien wurden in den frühen 2000er Jahren durchgeführt. Die Gesamtzahl der Patienten betrug 266, 133 in jedem Arm.

Die Einschlusskriterien der Studien unterschieden sich folgendermaßen:

- Ausgangwerte auf der HDRS-17 Skala:
  - 24 bis 26 in der rTMS-Gruppe
  - 25 bis 28 in der ECT-Gruppe
- AD- Einnahme:
  - 2 Studien: vorangegangener AD-Therapieversuch mit zwei oder mehr AD
  - 1 Studie: vorangegangener AD-Therapieversuch mit einem oder mehr AD, bzw. 1 Studie berichtete AD-Therapieversuche in der derzeitigen Episode
  - 2 Studien: Einschluss von PatientInnen mit vorangegangener ECT Therapie (keine Information zur AD Therapie)
  - 2 Studien: rTMS bzw. ECT unter AD Therapie
  - 2 Studien: medikamentenfrei
  - 2 Studien: Therapie mit Lorazepam oder Clonazepam

unterschiedliche Einschlusskriterien der verschiedenen Studien in Bezug auf Ausgangswerte, AD-Einnahme und Stimulationsparameter

- Stimulationsparameter:
  - Frequenz (10Hz bzw 20 Hz), Intensität (90 bis 110 %), die Anzahl der Stimulationen (20 bis 30-35), die Stimulationsdauer (2 bis 10 s), Zwischeninterval (20 bis 55 s), die Impulse pro Sitzung (408 bis 2.500), Anzahl der Sitzungen (10 bis 20). Gesamtzahl der gelieferten Impulse (4.080 bis 50.000).
  - Alle Studien verwendeten die *Figur 8* Spulen.

Klinische Wirksamkeit

rTMS vs sham

rTMS vs Sham

Im Durchschnitt verringerte rTMS die Punktezahl auf der Depressionsskala um etwa 2.31 Punkte mehr als die Scheinintervention (95 % CI 1.19-3.43, p <.001). Dies liegt allerding unter dem klinisch relevanten Schwellenwert von 3.5 Punkten.

Verbesserung in der Depressionsskala um 2,31 Punkte, klinisch nicht relevant

Das gepoolte Risikoverhältnis für die Remissionsrate über 12 Studien betrug 2.16 (95 % CI 1.42-3.29, p = 0.0003). Das gepoolte Risiko-Verhältnis für die Ansprechrate über 19 Studien betrug 1.82 (95 % CI 1.18-2.82, p = 0.0068).

Remissionsrate: RR 2.16 Ansprechrate: RR 1.82 zugunsten von rTMS

In Bezug auf allgemeine und psychische Gesundheit, gemessen mit dem SF-36 score, berichtete ein RCT [15] statistisch signifikanten Verbesserungen in der rTMS Gruppe. Auch in Hinblick auf QoL fand die Studie statistisch signifikante Verbesserung in der rTMS Gruppe, gemessen mit dem Q-LES-Q-Score.

QoL: 1 RCT berichtete signifikante Verbesserungen

rTMS vs ECT

Die gewichtete mittlere Differenz der Depressionswerte von der Baseline bis zum Ende der Behandlung betrug -5.97 Punkte (95 % CI -11.00 – (-0.94), p = 0.020) zugunsten von ECT, und damit höher der klinisch relevante Schwellenwert.

Verbesserung in der Depressionsskala um 5,97 Punkte in ECT Gruppe, klinisch relevant

Das gepoolte Risikoverhältnis für die Remission betrug 1.44 (95 % CI 0.64-3.23, p = 0.375) am Ende der Behandlung zu Gunsten von ECT. Diese Ergebnisse sind allerdings nicht signifikant und die Studien wiesen ein hohes Maß an Heterogenität auf (I^2 = 69.1 %, p = 0.039).

keine signifikanten Unterschiede zw. rTMS und ECT in Remissions- und Ansprechraten

Das gepoolte Risikoverhältnis Therapieansprechrate betrug 1.72 (95 % CI 0.95-3.11, p = 0.72). Wiederum waren diese Ergebnisse nicht signifikant, mit einem hohen Maß an Heterogenität der Studien (I^2 = 60.6 %, p = 0.079).

Die Selbstmordgedanken, gemessen sowohl mit BDI als auch HDRS Skala, sanken signifikant stärker in der ECT Gruppe als in der rTMS Gruppe.

geringere Selbstmordgedanken bei ECT

Sicherheit

rTMs vs sham

Die am häufigsten berichtete Nebenwirkung war Kopfschmerz. Die Rate der Kopfschmerzen reichte von 0 bis 60 % in der rTMS-Gruppe und 0 bis 50 % in der Scheingruppe. Krampfanfälle traten in keinen Studien auf, eine transiente kognitive Beeinträchtigung trat bei fünf PatientInnen (16.7 %) in der rTMS-Gruppe und einem Patienten (4.3 %) in der Scheingruppe ein.

keine schwerwiegenden NW berichtet, häufigste NW war Kopfschmerz

rTMS vs ECT

Es wurden keine schwerwiegenden Nebenwirkungen berichtet. Bei rTMS-PatientInnen waren Kopfschmerzen die häufigsten Nebenwirkungen, ECT-PatientInnen berichten keine unerwünschten Ereignisse.

bei PatientInnen mit ECT traten keine NW auf

Laufende Studien

Es gibt vier laufende Studien zu rTMS im Vergleich zur Scheinstimulation, aber keine laufenden Studien, die rTMS mit ECT vergleichen.

4 laufende Studien zu rTMS vs Sham

Kostenerstattung

Die Technologie wird in der Mehrheit der Länder, für die wir Informationen zur Verfügung hatten, sowie in Österreich, nicht zurückerstattet.

derzeit nicht erstattet

Diskussion

Die Gesamtqualität des Beweismaterials ist sowohl für Schein- als auch für ECT-Vergleichsstudien sehr gering.

sehr niedrige Qualität der Evidenz

Die methodischen Einschränkungen könnte die Empfehlung in Hinblick auf die Robustheit der Wirksamkeitsergebnisse erheblich beeinflussen. Diese Einschränkungen beinhalten variable Studienparameter (rTMS-Behandlungsprotokolle, die Definition der Remission, die Definition der TRD, Verwendung als Mono- oder Add-On-Therapie), das Bias Risiko (ein hohes Risiko Bias dem ECT-kontrollierte Studien auf Grund fehlender Verblindung), kleine PatientInnen Fallzahlen (sowohl im Schein- als auch in der ECT-kontrollierten Studie).

methodische Einschränkungen

Lebensqualität und PatientInnen Zufriedenheit wären wünschenswerte primär Endpunkte für Studien an therapieresistenter Depression; diese wurden jedoch nur von einer Studie berichtet. Des Weiteren fehlen Langzeitdaten zu Wirkung von rTMS.

QoL-Ergebnisse und PatientInnen Zufriedenheit in den Studien vernachlässigt

Empfehlung

Die Ergebnisse der Bewertung zeigen, dass rTMS im Allgemeinen sicher und gut verträglich ist. rTMS hatte einen kurzfristigen Effekt auf die Verbesserung der Depression im Vergleich zur Scheinintervention, der allerdings klinisch nicht relevant sein könnte. Follow-up Studien konnten keinen langanhaltenden Effekt von rTMS finden.

rTMS ist sicher und gut verträglich, effektiver als Scheinintervention

Die Wirksamkeit im Vergleich zu ECT zeigt einen Vorteil von ECT gegenüber rTMS in Bezug auf die klinisch relevante Verbesserung auf der Depressionsskala; jedoch gibt es keine signifikanten Unterschiede im Hinblick auf Ansprechrate und Remissionsrate. Die Qualität der Studien ist sehr niedrig, unter anderem bedingt durch die niedrige Fallzahl und hohe Heterogenität der Studien.

Wirksamkeit gegenüber ECT unklar

Aufgrund dieser niedrigen Qualität der Evidenz könnten neue Studienergebnisse die Effektschätzung erheblich beeinflussen. Weitere Studien, die Langzeitdaten zu rTMS untersuchen, sind notwendig, um die tatsächliche Wirksamkeit der Intervention zu bestätigen.

neue Studien mit Langzeitdaten von rTMS nötig um Wirksamkeit zu bestätigen

1 Scope

1.1 PICO question

Is repetitive transcranial magnetic stimulation (rTMS) in patients with treatment-resistant major depression as effective as or more effective than and as safe as or safer than sham stimulation or electroconvulsive therapy (ECT)?

PIKO-Frage

1.2 Inclusion criteria

Inclusion criteria for relevant studies are summarized in Table 1-1.

Einschlusskriterien für relevante Studien

Table 1-1: Inclusion criteria

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 [5, 7, 20-24] 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 [5, 21] 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.

Description	Project scope
Comparison	❁ **Sham** stimulation (with antidepressant medication or no medication) ❁ **ECT** Rationale: Comparator has been chosen based on information from EUnetHTA guidelines [25-27] and relevant published clinical guidelines [5, 7, 20-24], 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.
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 [5, 7, 20-24] and EUnetHTA guidelines [25-27].

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 Symptomatology, QoL quality of life*

2 Methods and evidence included

2.1 Research questions

Element ID	Description and technical characteristics of the technology
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?

Element ID	Health problem and current use of the technology
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?

Element ID	Clinical effectiveness
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?

Element ID	Safety
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?

2.2 Source of assessment elements

Bericht folgt HTA Core Model für REA

The selection of assessment elements is based on the HTA Core Model Application for Rapid Relative Effectiveness (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.

Literatursuche in 2 Schritten:

1. Suche nach sekundär Studien (HTA Berichte und SR) in 5 Datenbanken

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).

HTA Berichte und SRs von 2012-2016

qualitative Bewertung mittels AMSTAR

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. SRs 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 SRs. Details can be found in Table A-3 in Appendix 1. The Health Quality Ontario (HQO) HTA report [13] was selected for update.

2. Suche nach zusätzlichen primär Studien (RCTs) in 4 Datenbanken

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. 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)

Suche nach laufenden Studien zu rTMS

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 (CPGs) were also searched in the UptoDate database, through handsearch and consultation with clinical experts.

2.4 Study selection

2.4.1 Selection of systematic reviews

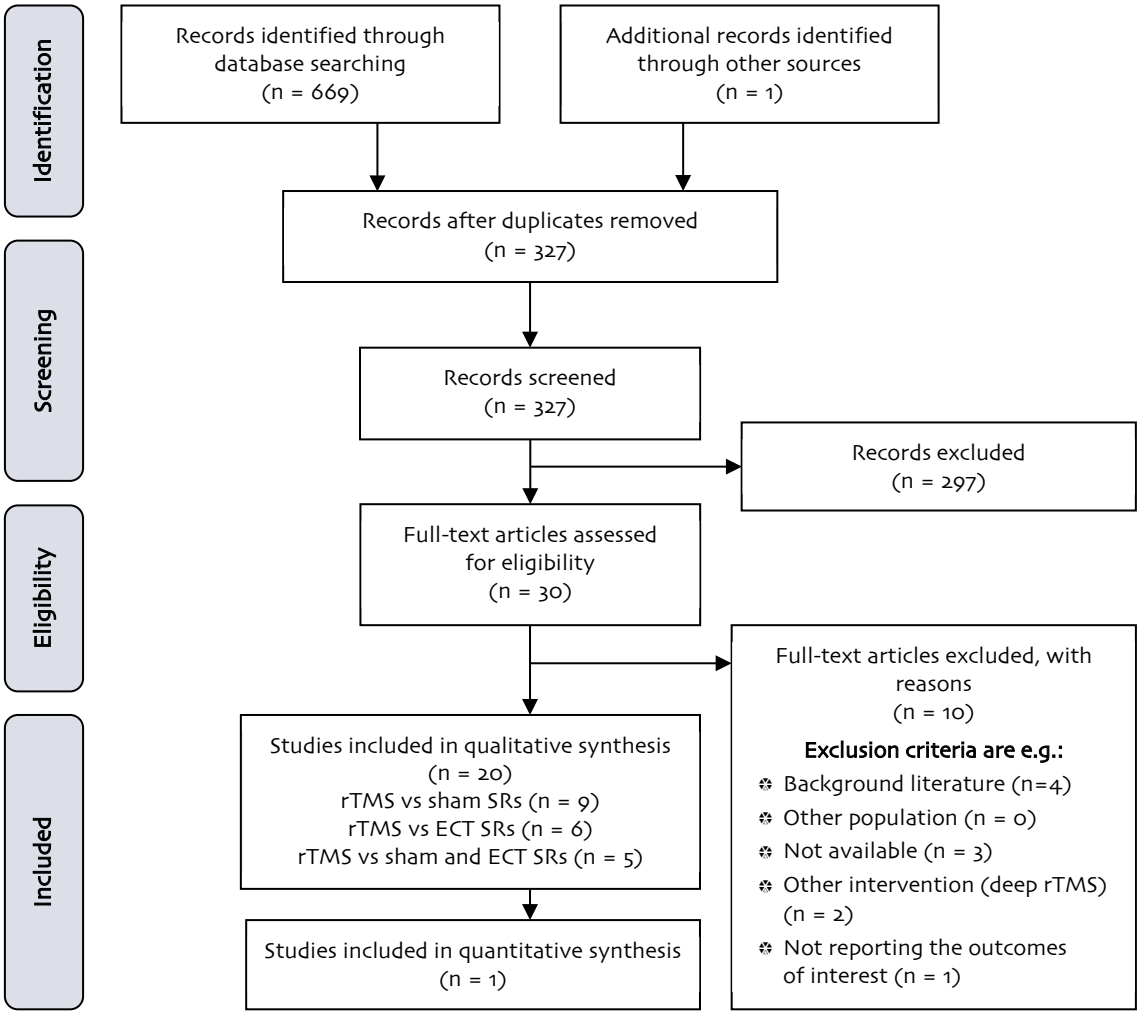

Figure 2-1: Flow chart for selection of systematic reviews

Literaturauswahl

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.

insgesamt 326 Publikationen identifiziert

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 various types of rTMS (HF, LF, mixed frequencies) applied 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 HQO 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.

20 SRs von denen 14 rTMS mit sham und 6 rTMS mit ECT, und 5 Studien beide Interventionen mit rTMS verglichen

Qualität mittels AMSTAR bewertet

2.4.2 Selection of primary studies

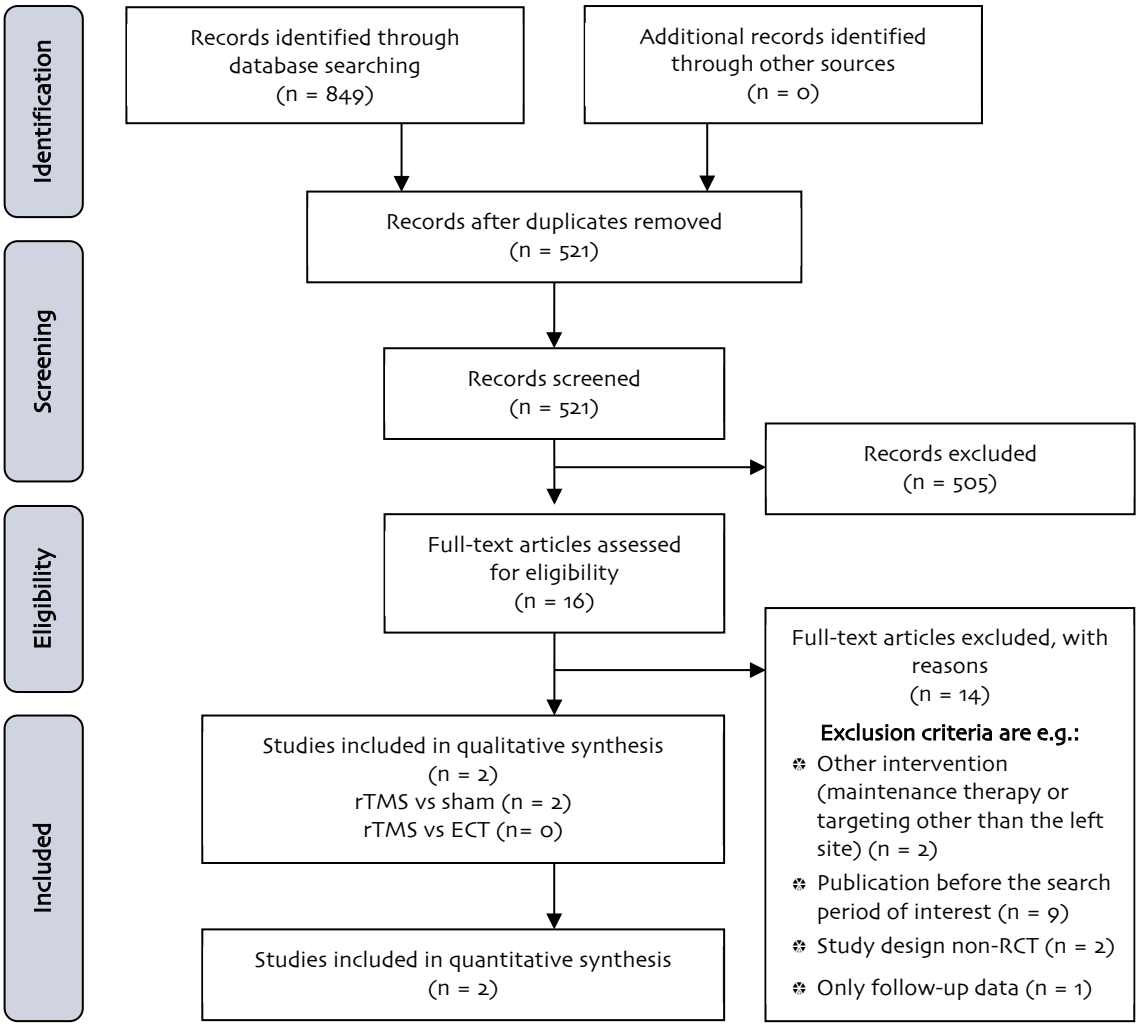

Figure 2-2: Flow chart for selection of primary studies

insgesamt 521 Primärstudien identifiziert

Primary studies in the period November 2014 – January 2017 were screened to identify new evidence. The search yielded 849 records, after deduplication 521 records remained for screening. A hand search identified no further studies. In total, two studies [14, 15] were selected that fulfilled our inclusion criteria and included within the present assessment. The two studies compared HF-rTMS to the left DLPFC with sham. No studies were found that compared active stimulation with ECT. Additionally, 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.

2.4.3 Selection of guidelines

Leitlinien relevanter Organisationen, im besonderen aus Österreich und Spanien

We identified guidelines via systematic search and hand search. The guidelines of the main scientific and professional organizations (APA, CANMAT, IFCN, RAZCP, and WSFBP) and the guidelines applicable by professional organizations of the author's (Austria, DGPPN) and co-author's (Spain, AVALIA-t) country of origin were selected to be included in the overview of available guidelines.

2.5 Quality rating of studies

AMSTAR zur Bewertung der Qualität der sekundär Studien

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 [25].

Zusammenfassung der Ergebnisse mit GRADE

For the assessment of the strength of evidence, the "Grading of Recommendations, Assessment, Development and Evaluation" – GRADE 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.

AGREE II zur Bewertung der Qualität der Leitlinien

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 completed 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 [28] using the package "meta" [29]. The HQO report 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.

Metaanalyse der zusammengefassten Ergebnisse mittels random-effects Model

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.

Veränderungen im Depressionspotential mittels ‚Hamilton Rating'

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.

Ansprechrate, Unterschiede im Risiko, Risikoquote als Gesamt-Effektschätzer mit 95 % Konfidenzintervallen

2.7 Description of the evidence

Table 2-1: 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. poststroke, 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

HQO Bericht zur Wirskamkeit und Sicherheit von rTMS

The HQO report [13] focused on the assessment of effectiveness and safety of rTMS in patients with treatment resistant depression. 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 2-1.

2 zusätzliche Primärstudien zur Bewertung der Wirksamkeit

Two new comparative primary studies were identified by updating the HQO report [13]. For answering effectiveness domain questions, we considered all studies included in the HQO report and the two new studies identified in the search update. To answer safety questions, we only considered studies from the HQO report that contained safety data.

nur Daten zu HF-rTMS und linker DLPFC extrahiert

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 and only extracted information in relation to HF-rTMS and sham and/or ECT.

Table 2-2: 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*

3 Description and technical characteristics of technology (TEC)

3.1 Results

3.1.1 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 [7, 10].

Transkranielle Magnetstimulation: nicht-invasive Neurostimulation des Gehirns, die kortikale Erregbarkeit beeinflussen kann

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) [5, 10].

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

kann als einfache oder Serie von Stimulationen verabreicht werden

The most typical technical parameters of rTMS are the following:

typische Parameter:

- 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 [5, 7]
  - 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 [7, 8].

- Frequenz (hoch oder niedrig)
- Intensität
- Dauer der Stimulationen
- Dauer zwischen den Stimulationen
- Anzahl der Stimulationen
- Anzahl der Pulse per Intervention

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 [9]. 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 [8].

unterschiedliche Protokolle, FDA-Standardparameter am häufigsten angewendet; effektivste Stimulationsparameter nicht bekannt

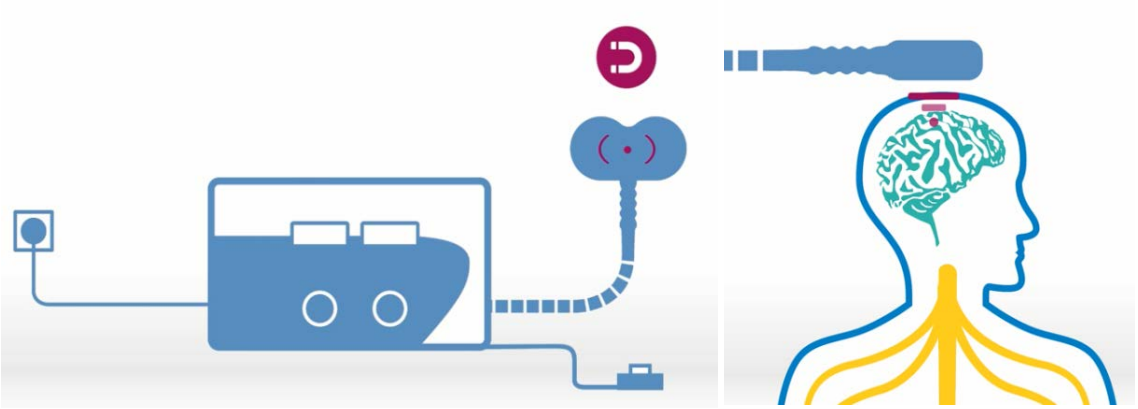

Figure 3-1: Mechanism of action of TMS; Source: submission file

Art und Ausrichtung der TMS Spule beeinflussen Wirkung

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 used for focal stimulation, when the stimulation zone should be only a few square centimetres large. 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 [30].

Kontraindikationen für rTMS

The use of rTMS is contraindicated 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.),
- 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 [7, 8, 10].

metallische Implantate, implantierte Medizinprodukte, erhöhter intrakranieller Druck, Schwangerschaft, Epileptische Anfälle, erhöhte Sensibilität auf Anfälle durch diverse Medikation

Screening Fragebogen für Kontraindikationen

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 [8].

Table 3-1: Features of the intervention

Proprietary name	Manufacturer	Technical features	Device class/UMDNS code
Magnetic stimulator Neuro-MS Magnetic stimulator Neuro-MS/D Big ring coil RC-01-150 Small ring coil RC-01-100 Figure-of-eight coil FEC-01-100	Neurosoft	**Magnetic stimulator Neuros-MS** delivers 20 Hz stimulation with 100% intensity with a number of pulses generated during one session – up to 10 000. The magnetic field than reach up to 4 tesla. **Magnetic stimulator Neuro-MS/D** possesses a cooling unit that allows performing long-term therapeutic impacts (also TMS with high frequency and intensity) without quick coil overheating. It provides the possibility to increase the maximal effective stimulation frequency (the frequency when each stimulus in series has 100% intensity of MT for most people) twice (up to 20 Hz) owing to extra power supply unit.	Class IIa/UMDNS 12-415
Magstim Rapid² 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 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
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

Proprietary name	Manufacturer	Technical features	Device class/UMDNS code
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: 5000, Nominal: 3000 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 [31-36].*

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 [37].

Comparators

Scheinstimulierung mit gekippter oder speziell angefertigter Spule

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 [38].

Verblingung ist fragwürdig bei erfahrenen PatientInnen

ausreichende Verblindung nur bei Erstanwendung gewährt

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 somato-sensory 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 [5, 38].

Elektrokonvulsionstherapie: künstlich ausgelöster Krampfanfall unter Generalanästhesie

Wirkmechanismus ungeklärt

Wirkung und Sicherheit von unterschiedlichen Parametern abhängig

ECT 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 functional connectivity. 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. ECT usually uses brief pulse width (0.25 to 2 ms) and duration (0.5 to 8 or more seconds) [11]. 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 [12].

sehr niedrige Mortalitätsrate, keine absoluten Kontraindikationen

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 [11].

kognitive Nebenwirkungen

ECT is frequently associated with cognitive impairment, including transient disorientation when recovering from ECT sessions, retrograde amnesia, and anterograde amnesia, and 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 [4, 11].

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

indiziert für PatientInnen mit unipolarer, therapieresistenter Depression

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 A-11 in Appendix 2.

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

Vorteile der rTMS: wenig invasive, keine Anästhesie nötig, keine Erhohlungsphase nötig, keine kognitiven Nebenwirkungen im Gegensatz zu 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 [4, 11].

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

erste FDA Zulassung in 2008 für NeuroStar TMS

TMS was developed by Barker in 1985 in Scheffield, 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 [4]. The first device to gain FDA approval was NeuroStar TMS Therapy System in 2008 [39].

neue Forschungsansätze: Bildverarbeitung mit PET und fMRI um Wirksamkeit von rTMS vorherzusagen

Currently, the use of functional imaging (PET and resting fMRI) or neuropsychological techniques (EEG) is a new development to help in better predicting the response to rTMS treatment through evaluating the cortical excitability. 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 [5, 7, 40].

TMS Apparatur für Anwendung zuhause

Another novelty currently tested is an oscillating weak TMS device, which aims to enable home delivery of TMS (under a doctor's prescription) that is unlikely to cause seizures [30].

verschiedene rTMS Variationen und Adaptierungen

There are several experimental techniques tested representing variations of rTMS, including the following:

- *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. [8].

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.

Scheinstimulations-Spulen seit 2000 verfügbar

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].

ECT als Therapie seit 1930ern verwendet

[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 [7, 8, 41].

Erst-Therapieeinstellung durch ÄrztInnen

in ambulantem Setting oder niedergelassenem Bereich

rTMS is administered on an ambulant setting in a hospital or appropriately equipped outpatient clinic. One session is delivered daily, 5 times a week. Administration is labour-intensive and time-consuming for both the patients and clinicians. [4, 7]. A session lasts typically 30-40 minutes [8]. The course of rTMS treatment lasts from 10 to 30 sessions. 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 [11].

Therapiedauer:
10 -30 Sitzungen
1 Sitzung dauert 30-40 Minuten,
5 x pro Woche

ECT: verschiedene SpezialistInnen erforderlich
1 Sitzung dauert 25-40 Minuten

Anwendung im Krankenhaus, zunehmend auch ambulant

2-3 x pro Woche

ECT requires a number of different specialists to be involved. The staff should comprise of an anaesthesiology nurse, a psychiatric nurse, plus 4 untrained nurses or nursing assistants, an anaesthesiologist, a psychiatrist, and an operating department assistant. According to clinical experts, one ECT session 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 [20]. ECT is typically conducted on inpatients, but outpatient (ambulatory) ECT practice is growing, largely because of its increasing use for continuation and maintenance treatment [23]. 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 [11].

[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?

Equipment für rTMS: Impulsgenerator und Spule

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 patient's head [7, 8, 10].

Equipment für ECT: Generalanästhesie, Muskelrelaxantien, Aufwachraum

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. 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 [12].

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

Details zur Erstattung von rTMS in Appendix 2

Detailed information on the reimbursement status/recommendations can be found in Table A-12 and Table A-13 in Appendix 2.

4 Health problem and current use of the technology (CUR)

4.1 Results

4.1.1 Overview of the disease or health condition

[A0002] – What is treatment-resistant major depressive disorder?

therapieresistente Depression: schwere Depression ohne Ansprechen auf medikamentöse Therapie mit Antidepressiva

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.

Therapieansprechen durch Verbesserung in Depressionsskalen gemessen

- 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) [1].

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

Risikofaktoren:

- Komorbidität
- chronischer Schmerz
- Medikation
- Psychiatrische Erkrankungen
- Substanzmissbrauch
- Persönlichkeitsstörungen
- Suizidalität
- junges Alter bei Erstdiagnose
- Wiederkehrende depressive Phasen
- niedrigen sozioökonomischen Status
- Geschlecht
- Familienanamnese

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 [3].

- 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 [1, 3].

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

Symptome entwickeln sich über Wochen, oft mit generalisierter Angst, Panikattacken, etc.
Dauer der depressiven Phase variiert stark

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 three episodes, the risk of recurrence is close to 100% in the absence of prophylactic treatment. The course of recurrent major depressive episodes also varies [20].

4.1.2 Effects of the disease or health condition

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

Selbstmordversuche,

hohe Komorbidität

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 [20].

Medikationsbezogene Nebenwirkungen

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 [42]. 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?

schwere Depression laut WHO Platz 2 der verheerendsten Krankheiten für die Gesellschaft

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 [43].

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 [20, 43].

hohe soziale, direkte und indirekte Kosten durch Arbeitslosigkeit, Produktivitäts-einschränkungen etc.

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 [42, 44].

zusätzlich: hohe medizinische Kosten

4.1.3 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)

Diagnose mittels DSM-IV-TR

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 [1].

andere psychiatrische Erkrankungen müssen ausgeschlossen werden

As underpinned by several studies, approximately 50% of MDD patients do not benefit from the first course of antidepressant treatment [4]. 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 [6]. Thase and Rush developed a staging system that is an aid in the application of treatment strategies in a stepwise fashion.

50 % der MDD PatientInnen: keine Verbesserung durch Erst- Antidepressiva Verschreibung

TRD: Misserfolg bei mindestens 2 verschiedenen antidepressiven Therapien

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 4-1: Thase-Rush Treatment-Resistant Depression (TRD) Staging Method. Source: [44]

Ausschluss einer Pseudo-Therapieresistenz durch zB. fehlende Compliance, schlechte ÄrtzInnen-PatientInnen Beziehung etc. wichtig

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 [3, 44].

adäquater Therapieversuch sollte 6-12 Wochen dauern; bei weniger als 25 % Verbesserung Wechsel der Therapie

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 [45].

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

keine spezifische Leitlinie zu TRD

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 A-2 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.

5 Hauptstrategien für die Behandlung von 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 [46]:

1. Medikations-optimierung
2. Wechsel in Antidepressiva
3. Kombinations-therapien
4. zusätzliche Wirkstoffe die Wirkung der Antidepressiva verbessern können

1. *optimization:* aximize 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 antidepressant; 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, psychostimulants, 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)

5. somatische Therapien

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*.

1st-Line Therapie: SSRI

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

2nd-Line Therapie: Änderung in Antidepressiva, Kombinationstherapien, Zusatz von Wirkstoffen die Antidepressiva Wirksamkeit erhöhen

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:

3rd-Line Therapie: rTMS, ECT und andere somatische Therapien

- rTMS
- ECT
- Other somatic therapies e.g. VNS, DBS
- Augmentation with omega-3 fatty acids, folate, S-adenosyl methionine, or pramipexole [44, 45, 47].

4.1.4 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 [44]. 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 [5].

PatientInnen mit unipolarer, therapieresistenter Depression

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

Prävalenz der TRD unbekannt

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) [3-5, 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 [5, 6, 44].
- 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% [1, 44].

Österreich: 120.00-140.000 PatientInnen mit Depression; 8.400-17.400 TRD

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 and achieve remission [48]. 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 with information on the utilization of rTMS by the manufacturers.

5 Clinical effectiveness (EFF)

5.1 Results

5.1.1 Included studies

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 [16]. A total of 1,180 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 [49, 50] 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 [16, 51-53] 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 [7]; they were also kept in the analysis.

1 sekundär Studie mit 23 RCTs und 2 zusätzliche RCTs erfüllten Einschlusskriterien

1.180 PatientInnen 615 bekamen rTMS Therapie

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 s. 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 s. All studies used the figure 8 coil.

Ausgangswerte der HDRS-17 Skala variierten von 19-28 in der rTMS Gruppe und 21-27 in der Kontrollgruppe

in 17 Studien erhielten PatientInnen rTMS und Antidepressiva; in 8 Studien nur rTMS Therapie

Stimulationsfrequenz von 5-20 Hz, 15-75 Stimulationen per Sitzung

alle Studien verwendeten ‚figure 8' Spulen

Details of the RCTs can be found in evidence tables Table A-5 in Appendix 1.

rTMS vs ECT

6 Studien verglichen rTMS und ECT

insgesamt 266 PatientInnen, 133 pro Interventions und Kontrollgruppe

2 Studien ohne Begleitmedikation

Ausgangswerte der HDRS-17 Skala variierten von 24-26 in der rTMS Gruppe und 25-28 in der ECT Gruppe

Stimulationsfrequenz von 10-20 Hz, 20-35 Stimulationen per Sitzung

alle Studien verwendeten ‚figure 8' Spulen

Six studies were found by authors of the HQO report 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 [17, 18]. Four studies reported that the outcome assessors were blinded, in two studies they were not blinded, of which one study [54] did not comply with the safety standards and therefore was not included in the meta-analysis. 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 RCTs can be found in evidence tables Table A-6 in Appendix 1.

5.1.2 Mortality

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

3 Studien berichteten Daten zu Suizidalität

rTMS vs ECT: höhere Verminderung bei ECT

jeweils ein Selbstmordversuch in der rTMS und der Kontrollgruppe

Three studies in the HQO report included data on suicide scores or suicidal ideations. We identified no new studies reporting on suicide. One of these studies [19] compared rTMS with ECT. The suicide score decreased from mean (SD) 1.5 (0.8) to 1.2 (0.9) as measured by BDI (Beck depression inventory) 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 [16, 55] and reported that no death occurred, but a single suspected suicide gesture in the sham group [16] and in the active stimulation group [55] was observed respectively.

5.1.3 Morbidity

[Dooo5] – 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 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).

rTMS um durchschnittl. 2.31 Punkte höhere Verbesserung in Depressionsskala

jedoch erst ab mehr als 3.5 Punkten klinisch relevant

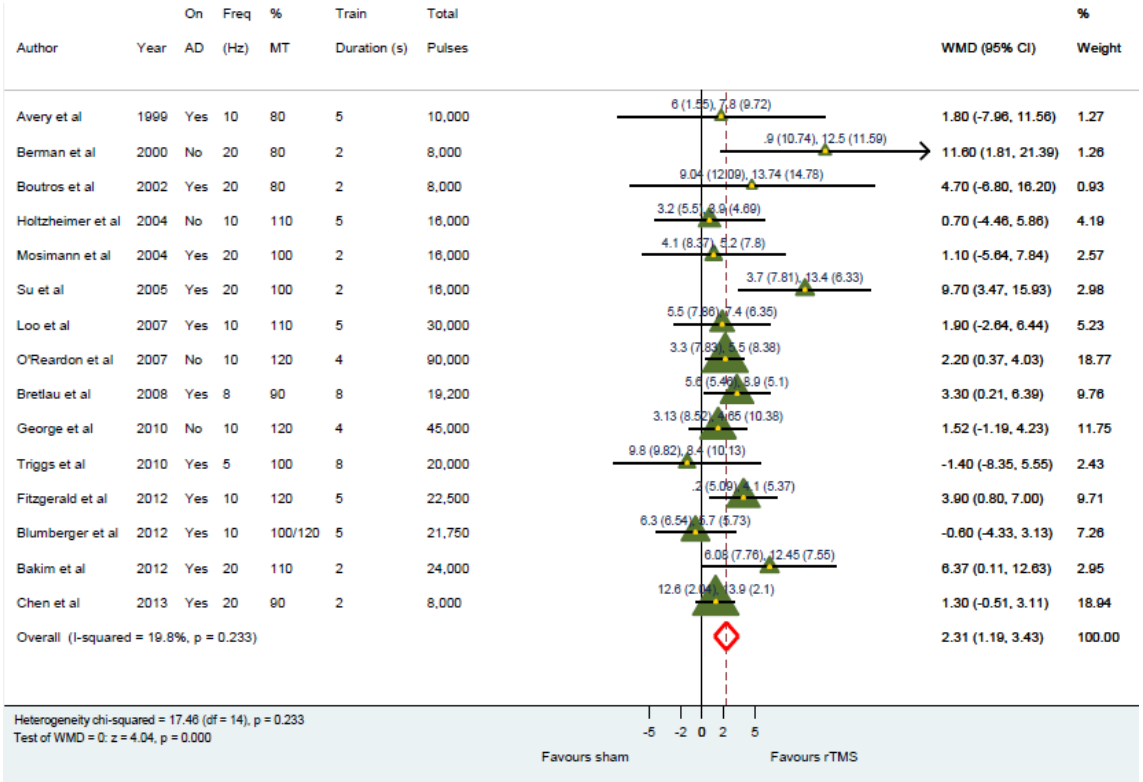

Figure 5-1: Weighted mean difference: rTMS vs sham; Source: HQO

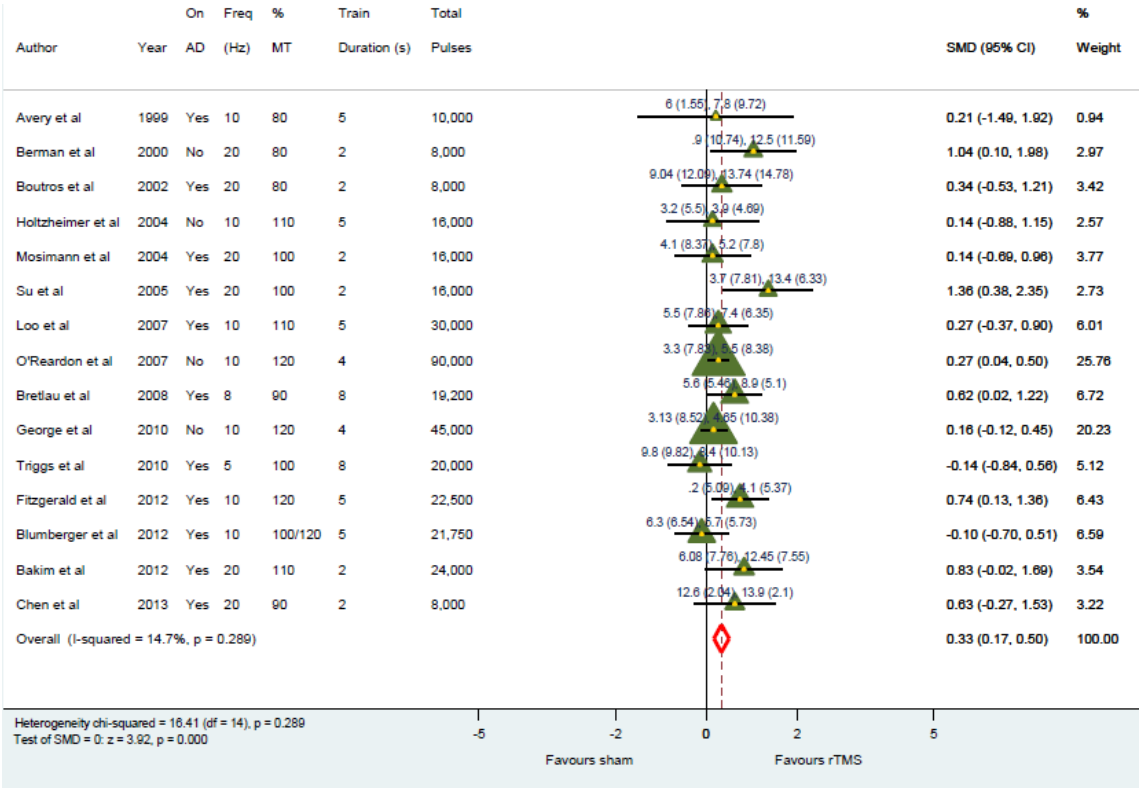

Figure 5-2: Standardized mean difference: rTMS vs sham; Source: HQO

rTMS vs ECT

ECT um 5.97 Punkte Verbesserung in Depressionsskala, Unterschied klinisch relevant; hohe Heterogenität der Studien

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 -11.00 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.

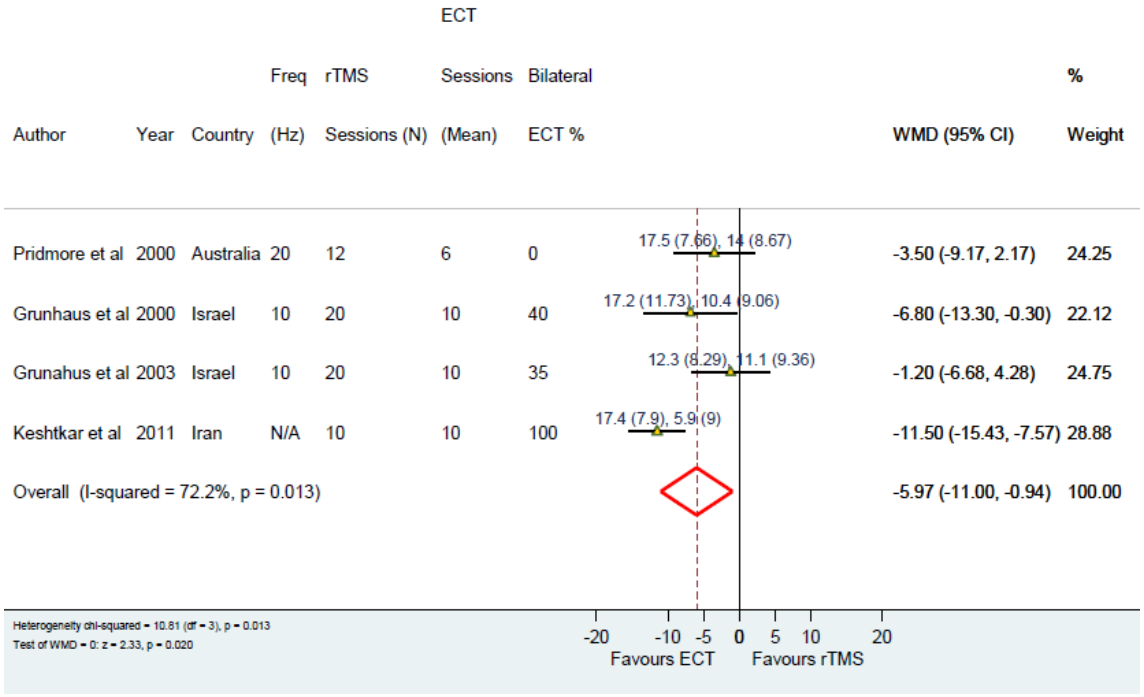

Figure 5-3: Weighted mean difference: rTMS vs ECT; Source: HQO

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).

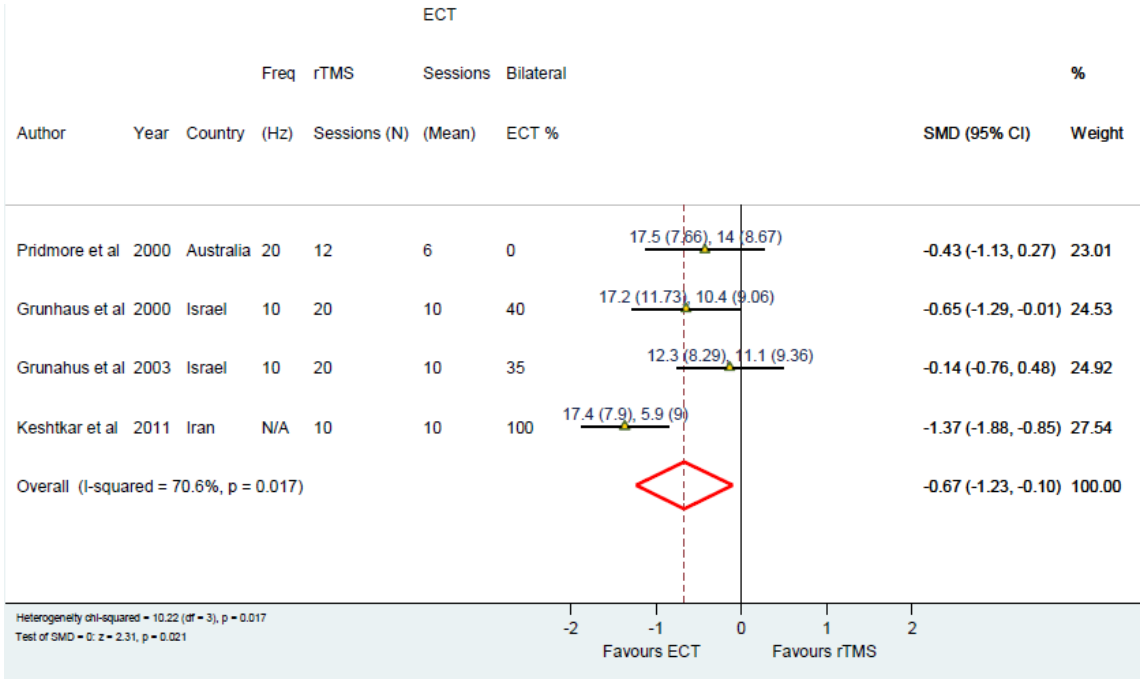

Figure 5-4: Standardized mean different: rTMS vs ECT; Source: HQO

[Dooo6] – How does rTMS affect progression (or recurrence) of treatment-resistant major depressive disorder?

rTMS vs sham

Remissionsraten: aus 12 Studien, RR: 2.16 (1.42-3.29)

Remission rates were reported in the HQO report in 13 studies. The pooled risk ratio has been calculated only for the ones that complied with the safety standards, hence, two studies [49, 50] 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 [56], no patients achieved remission in either arm and therefore, it did not contribute to the summary estimate.

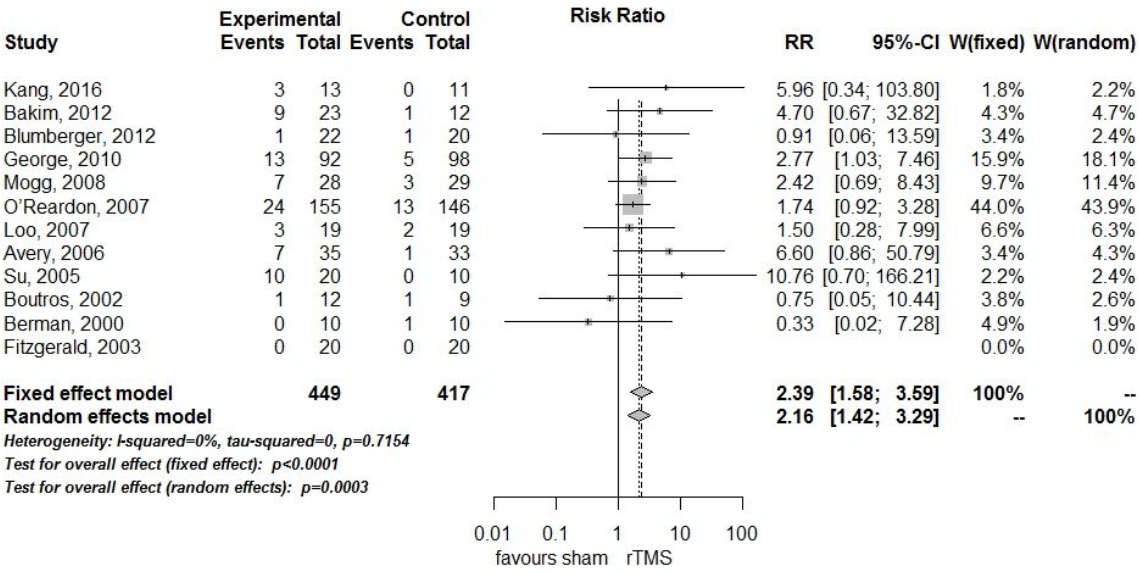

Figure 5-5: Remission rate at the end of treatment: rTMs vs sham

10 % höhere Remissionsraten in rTMS Gruppe

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.

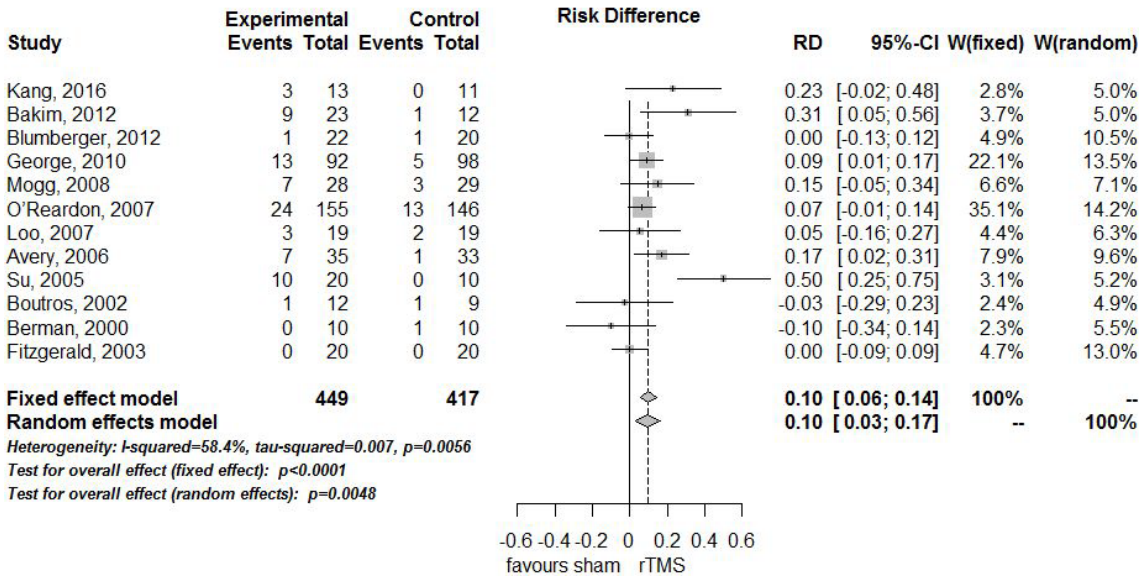

Figure 5-6: Risk difference for remission rate: rTMS vs sham

Ansprechrate: aus 19 Studien, RR 1.82 (1.18-2.82)

Response rates were reported in 20 studies in the HQO report, but only 18 studies complied with the safety standards (two studies [49, 50] 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).

13 % Verbesserung der Ansprechrate bei rTMS

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 [57] and in Fitzgerald 2003 [56], no patients responded to the treatment in either arm, therefore, it did not contribute to the summary estimate.

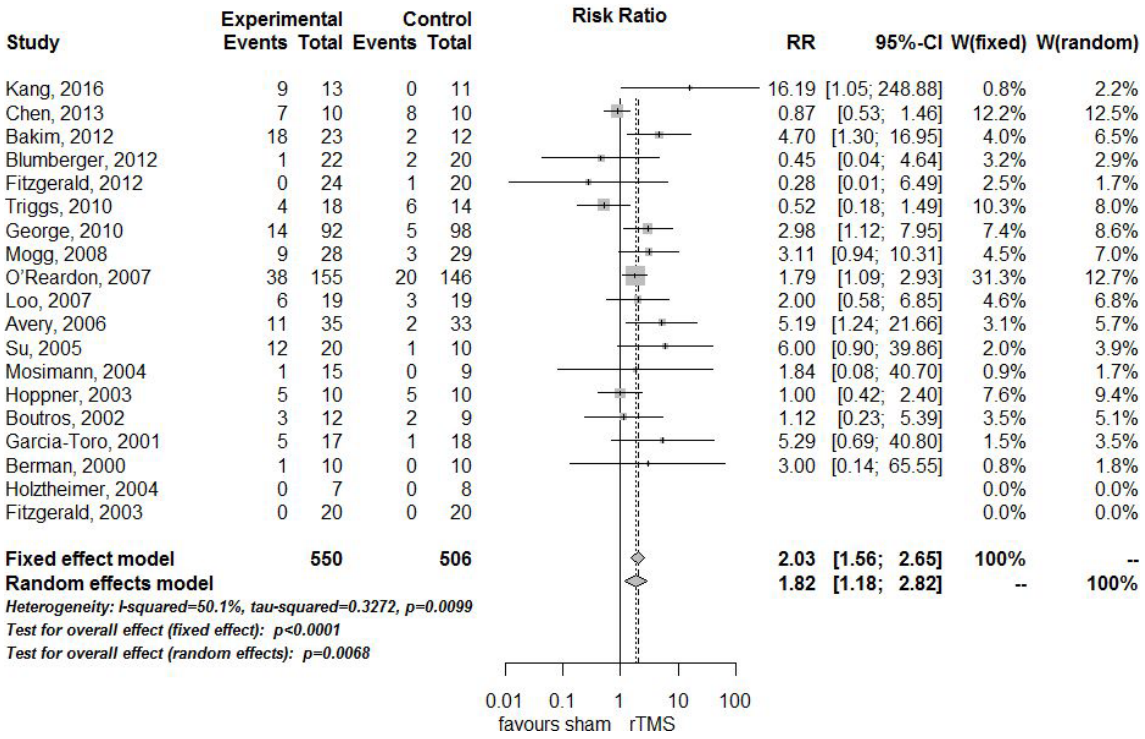

Figure 5-7: Response rate at the end of treatment: rTMS vs sham

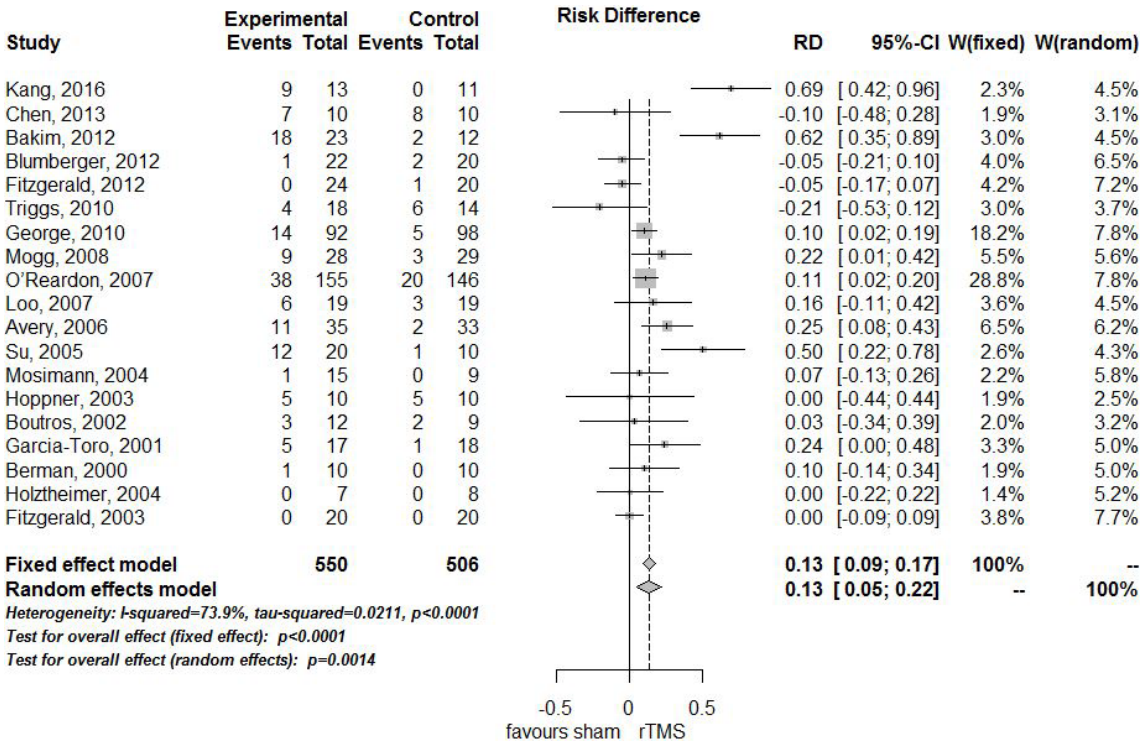

Figure 5-8: Risk difference for response rate: rTMS vs sham

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). The pooled risk ratio did not reach significance level, as the studies used different ECT protocols and were very heterogeneous.

Remissionsrate aus 6 Studien, kein signifikanter Unterschied zwischen rTMS und ECT

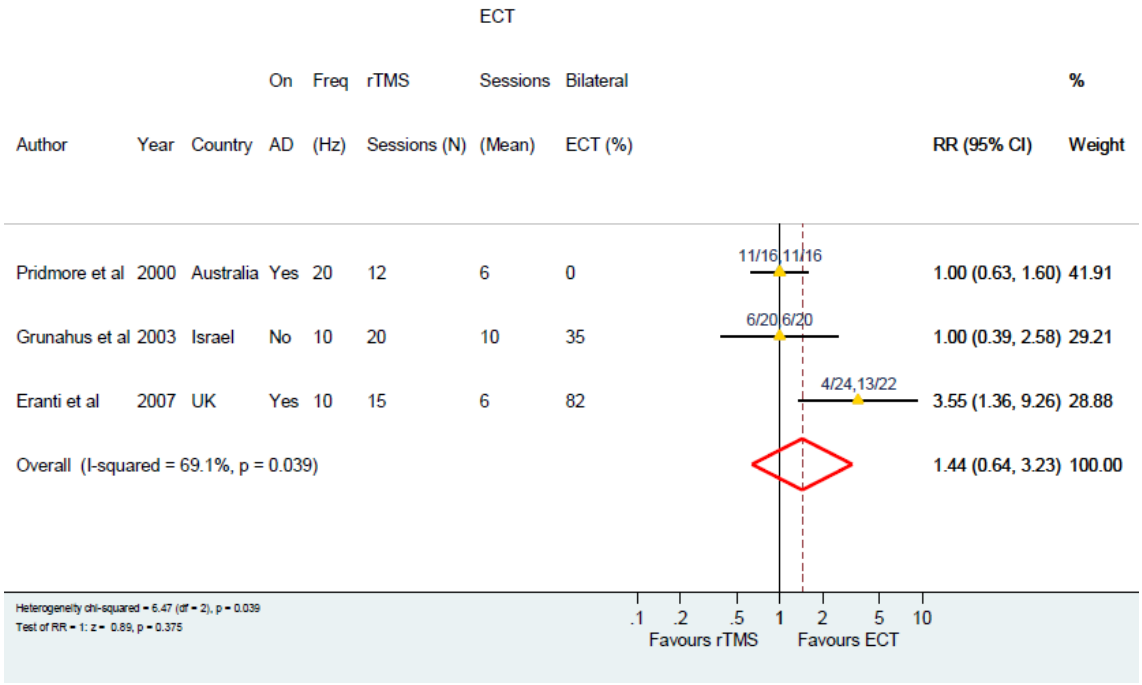

Figure 5-9: Remission rate: rTMS vs ECT; Source: HQO

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.

Ansprechrate: keine signifikater Unterschied zwischen rTMS und ECT

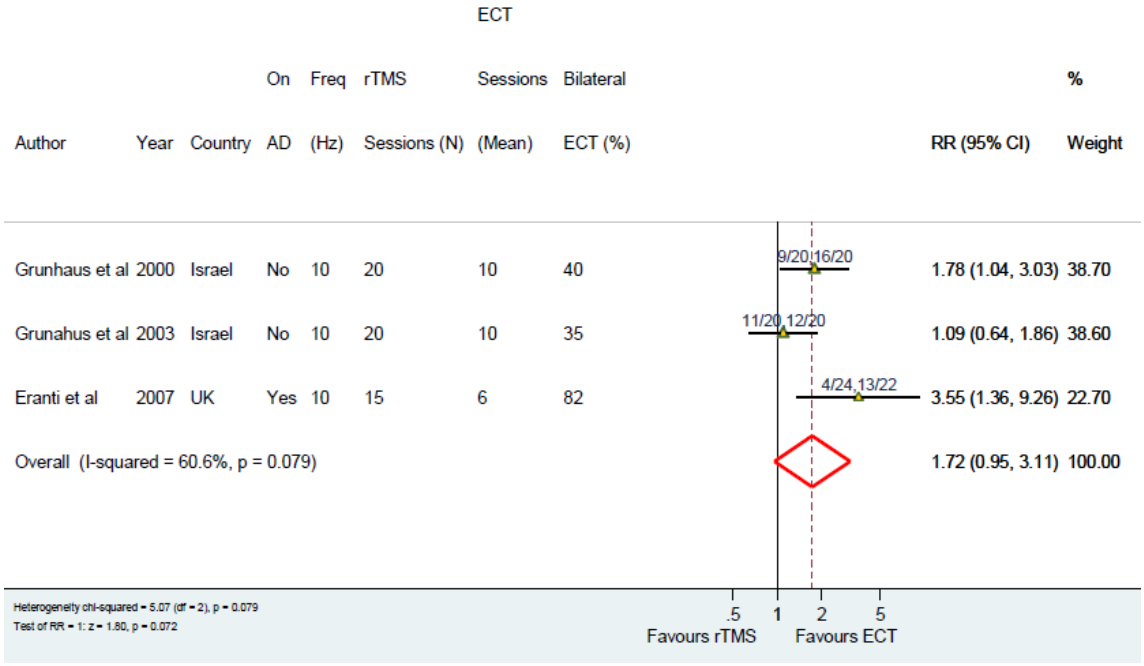

Figure 5-10: Response rate: rTMS vs ECT; Source: HQO

[Do011] – What is the effect of rTMS on patients' body functions? and [Do016] – How does the use of rTMS affect activities of daily living?

nur 1 Studie für diese Forschungsfrage; mit SF-36 Skala bewertet

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. On the 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 not statistically significant.

signifikante Verbesserungen in physische Funktionsfähigkeit und Körperschmerz

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 intervention 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.

5.1.4 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 improvements on the SF-36 subscale of general health and the Q-LES-Q favouring rTMS were also reported at the 6-months follow up.

Generelle QoL: Verbesserung in der rTMS Gruppe in der 4ten und 6ten Therapiewoche

[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.

Krankheitsspezifische QoL: Verbesserung in psychischer Gesundheit nach der 4ten und 6ten Therapiewoche

5.1.5 Satisfaction

[D0017] – Were patients satisfied with rTMS?

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

keine Evidenz verfügbar

6 Safety (SAF)

6.1 Results

6.1.1 Included studies

The same secondary studies used in the Clinical Effectiveness domain were assessed for inclusion in the Safety domain. We included 1 SR, which was the most recently published SR that met our inclusion criteria. The review was updated within the present assessment and two additional primary studies were included.

rTMS vs sham

In the updated HQO report, 16 studies reported on adverse events. One study provided scores on a side effect scale [58].

16 Studien des HQO Assessments berichteten AEs für rTMS vs Scheinintervention

rTMS vs ECT

Only one study did not report in any form of adverse events [54]. Only one study reported on seizure [19, 59], there studies reported on headache [19, 59, 60], one on device-related insomnia [60], one on transient impairment of working memory [19] and two studies used side-effects rating scores [18, 61], but did not report explicitly which side-effects occurred. 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.

diverse Sicherheitsendpunkte berichtet, nur 1 Studie berichtete keine AE

6.1.2 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 [62, 63] and occurred in five patients (16.7%) in the rTMS group and one patient (4.3%) in the sham group. Induced electrical current in implanted devices was not reported in any of the studies.

häufigste NW: Kopfschmerz (bei bis zu 60 % rTMS vs 50 % Sham) Schmerzen, Unbehagen der Kopfhaut (bis zu 80 % in rTMS und 20 % in Sham) Augenprobleme (bis 21 % bei rTMS und 1.9 % bei Sham)

rTMS vs ECT

No serious safety concerns were identified. The most common side-effect was headache in rTMS-treated patients with a range of 3-25% across studies. No adverse events occurred in ECT-treated patients.

keine SAEs AEs: Kopfschmerz keine AEs bei ECT Gruppe

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

keine Evidenz vorhanden

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?

keine Evidenz vorhanden

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?

keine Evidenz vorhanden

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?

Aufzeichnungen von AEs und SAEs für rTMS und ECT notwendig

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 6-1: Frequency 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	[16, 51-53, 55, 56, 63-69]	144 (32)	45 (11)	0-60	0-50	[19, 59, 60]	9 (12.3)	0	3-25	0
Scalp discomfort	[16, 51, 52, 56, 62, 63, 65, 68, 70]	70 (19)	16 (5)	4.5-33	0-21	NA	NA	NA	NA	NA
Vertigo	[52, 55, 56, 63, 64, 71]	7 (3.3)	8 (3.9)	0-16.7	0-14	NA	NA	NA	NA	NA
Seizure	[16, 49-51, 64, 65, 67, 68, 70-72]	0	0	0	0	[19, 59]	0	0	0	0
Gastrointestinal problems	[16, 52, 55, 62, 63, 68]	25 (8)	7 (2.4)	5-22	0-22	NA	NA	NA	NA	NA
Eye problems	[16, 55, 63, 68]	15 (7.2)	3 (1.6)	5.6-21	0-1.9	NA	NA	NA	NA	NA
Face twitching	[16, 52, 63, 68]	15 (5.3)	6 (2.2)	0-20.6	0-3.2	NA	NA	NA	NA	NA
Insomnia	[52, 63, 65]	9 (6.7)	11 (8.2)	4.5-7.6	0-10	[60]	2 (10)	0	0	0
Syncope	[52, 63]	10 (9)	6 (5.4)	5-27.8	4-14	NA	NA	NA	NA	NA
Hypomania	[53, 68]	2 (5.1)	0	0	0	NA	NA	NA	NA	NA
Cognitive impairment	[62, 63]	5 (16.7)	1 (4.3)	0-41.7	0-7	[19]	0	0	0	0
Death	[16]	0	0	0	0	NA	NA	NA	NA	NA

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

7 Quality of evidence

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [105] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [105].

GRADE uses four categories to rank the strength of evidence:

- *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;
- *Very low* = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in Table 7-1.

entscheidene Endpunkte für Wirksamkeit und Sicherheit

For effectiveness related endpoints response and remission rates were considered critical, for safety-related endpoints serious adverse events were defined as critical outcomes. The mean difference in depression scores was considered an important, but not critical outcome. 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.

Stärke der Evidenz für rTMS im Vergleich zu sham und ECT sehr niedrig

Overall, the strength of evidence for the effectiveness and safety of rTMS in comparison to both sham and ECT is very low.

Table 7-1: Evidence profile: efficacy and safety 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 7-2: Evidence profile: efficacy and safety 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%)	0/53 (0.0%)	**RR 1.13** (0.02 to 55.96)	**2 more per 1 000** (from 18 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]

Nomenclature for GRADE table:

Limitations: 0: no limitations or no serious limitations; -1: serious limitations

Inconsistency: NA: Not applicable (only one trial); 0: no important inconsistency; -1: important inconsistency

Indirectness: 0: direct, no uncertainty, -1: some uncertainty, -2 major uncertainty

Other modifying factors: publication bias likely (-1), imprecise data (-1), strong or very strong association (+1 or +2), dose-response gradient (+1), Plausible confounding (+1)

8 Discussion

The aim of this report was to assess the clinical effectiveness and safety of rTMS compared to sham stmulation or ECT. We considered studies that applied unilateral high-frequency stimulation to the left DLPFC in both the sham controlled and the ECT comparison studies.

Forschungsschwerpunkt: Wirksamkeit und Sicherheit von rTMS

Interpretation of findings

We identified one SR and two RCTs to assess the clinical effectiveness and safety of rTMS for patients with TRD. A total of 1180 patients were analysed in the studies that compared rTMS with sham stimulation, and 266 in the studies that compared rTMS with ECT.

1 SR und 2 RCTs
Gesamtzahl der PatientInnen:
1180 (rTMS vs sham)
266 (rTMS vs ECT)

The body of evidence indicates that rTMS is generally safe and well-tolerated. The most serious adverse effect is seizure, which was not observed in any of the studies. As described in the safety guideline [7], 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.

rTMS ist sicher, gut toleriert

TMS 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. In comparison with ECT, the critical endpoints remission and response rates showed no statistically significant difference. However, the mean difference in depression scores was statistically and clinically significant favouring ECT.

wirksamer als Scheinintervention, Wirksamkeit gegenüber ECT unklar

Study quality, validity and overall level of evidence

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

Qualität der Evidenz niedrig bei beiden Komperatoren

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. 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 or bilateral in less than 40% of patients.

Methodologische Limitierungen: Unterschiedliche Behandlungsprotokolle mit verschiedenen Frequenzen, Anzahl an Impulsen etc.

Definitionen zu entscheidendem Endpunkt Remission sehr unterschiedlich in Studien

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.

Studie, die rTMS mit ECT verglichen hatten hohes Biasrisiko, keine ausreichende Verblindung

Most of the included studies that compare rTMS and ECT 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. Most of the sham controlled studies had a combination of unclear and low risk of bias, and a few had 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.

Fallzahlen im Allgemeinen zu klein um konkrete Aussagen zur Wirksamkeit zu machen

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

eventuelle Beeinflussung der Ergebnisse durch anatomisch inkorrekte Anbringung

The treatment intensity is influenced by the coil to cortex distance. The standard protocol, followed by the earliest studies, applied the 5 cm method. Recent studies have re-evaluated this method and found that it may be anatomically incorrect and therefore limiting the treatment potential of rTMS. If the coil is not placed at the right area, 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. On the contrary, if stimulation is delivered at a too low intensity, the efficacy of the treatment might be compromised.

nur wenige Studien berichteten relevante Sicherheitsendpunkte

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 [18] measured cognitive impairment, which is the most common adverse event in ECT therapy.

Factors that may influence the external validity

hohe Heterogenität der Definition für TRD

There was heterogeneity in how the studies defined TRD (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.

in manchen Studien als Monotherapie, in anderen als Zusatz zu AD Therapie

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.

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 [11], 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 [4, 24].

kein Therapie-Algorithmus für TRD vorhanden
daher Vergleich mit ECT als Standardtherapie;

Potenzial als komplementäre Intervention in frühen Stadien der TRD und vor ECT denkbar

Relevance of the outcomes assessed to the potential patient-relevant benefits

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. Some studies reported relapse, but we have no information how the treatment impacted patients' lives in terms of daily functioning, returning to work etc.

QoL wurde nur von einer Studie berichtet

keine Langzeitdaten

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.

trotz der hohen Relevanz wurde PatientInnen Zufriedenheit nicht berichtet

Some ethical, organizational and social aspects are also associated with the use or non-use of rTMS and can be found in Appendix 3.

Evidence gaps and ongoing studies

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.

keine Subgruppenanalyse von rTMS als Monotherapie oder Kombinationstherapie (mit AD)

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. There is a need for more studies with long-term (6 month) follow-up data to support the evidence on long-term clinical effectiveness.

nur wenige Follow-up Daten berichtet, nur bis zu 6 Monate keine Langzeitdaten vorhanden

We identified four ongoing studies investigating rTMS compared to sham with the number of enrolled patients ranging from 28 to 168. The estimated completion date of three trials has passed in 2016 or earlier, but no results have been published yet. The fourth study has not registered its completion date. We also identified five studies comparing DTMS with sham or other rTMS (LF, HF) techniques. DTMS is delivered with the H-coil that can reach deeper brain areas than the conventional coils. Some other novelties are also being investigated in clinical trials, for example the sTMS, aTMS, and TBS.

4 laufende Studien für rTMS vs Sham
5 Studien zu DTMS und rTMS

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Table 9-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
X	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence indicates, that the assessed technology rTMS is more effective than and as safe as sham. 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. However, the quality of evidence is considered very low. New study results will potentially influence the effect estimate considerably.

rTMS wirksamer als und gleich sicher wie Scheinbehandlung

The current evidence is not sufficient to prove that rTMS is as effective and safe as ECT. There is evidence that ECT is more effective in reducing depression scores, however, no significant differences were found in terms of remission and response in comparison to rTMS. No serious safety concerns were observed; side effects appear to be equivalent between rTMS and ECT.

unzureichende Evidenz um die Wirksamkeit und Sicherheit gegenüber ECT zu belegen

Due to the low quality of evidence of the included studies, we recommend rTMS for patients with TRD with restrictions. The technology might be an option for patients in the early stages (Stage 1 or 2) of TRD. The place in the treatment hierarchy could precede more invasive interventions such as ECT, VNS and DBS.

Qualität der Evidenz niedrig, Empfehlung mit Einschränkung

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.

4 laufende Studien

The re-evaluation is recommended only if several high-quality clinical trials with sufficient number of enrolled patients (n>300) will be completed and if they provide additional long-term data on safety and/or effectiveness outcomes.

Re-Evaluierung: nur bei Studien mir ausreichender Fallzahl und Langzeitdaten

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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. *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	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
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 o:"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.	o
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 Editorial Independence: 0,67 Global quality of the CPG: E1: 6 E2:	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. 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.	B 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 A-2: 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
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

Society/organisation issuing guidance	Date of issue	Quality appraisal (AGREE II)	Methodology (evidence and recommendations)	Summary of recommendation	Level of evidence
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
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

Society/organisation issuing guidance	Date of issue	Quality appraisal (AGREE II)	Methodology (evidence and recommendations)	Summary of recommendation	Level of evidence
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.	
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 anti-depressant 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 Psychiatris*

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)
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)

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)
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 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.	rTMS (L, R, B) vs sham rTMS (L, R, B)	Standardized mean difference in depression scores	I*nclusion:* sham controlled RCTs with parallel design, HAMD, BDI or MADRS scales, pts with MDD (diagnosed according to DSM-IV or ICD-10)	Aguirre 2011, Bakim 2012, Blumberger 2012, Chen 2013, Fitzgerald 2012, George 2010, 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	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)
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: 1646 pts, 32 RCTs	To assess the clinical relevance of the 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	Avery 2006, Bakim 2012, Bretlau 2008, Chen 2013, Garcia-Toro 2001, Garcia-Toro 2006, George 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	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)
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 ≥ 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)
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)

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)
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]	Economic evaluation	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, J anicak 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 outcomes 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 A-5: Characteristics of randomised controlled studies comparing rTMS with sham rTMS

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 therapeutic 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.
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

Study characteristics						
Author, year, reference number	**Kang, 2016 [14]**	**Chen, 2013 [94]**	**Bakim, 2012 [51]**	**Blumberger, 2012 [65]**	**Fitzgerald, 2012 [72]**	**George, 2010 [52]**
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 treatment 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, ferromagnetic 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
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

[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]**
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
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

Study characteristics						
Author, year, reference number	**Kang, 2016 [14]**	**Chen, 2013 [94]**	**Bakim, 2012 [51]**	**Blumberger, 2012 [65]**	**Fitzgerald, 2012 [72]**	**George, 2010 [52]**
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						
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 Schizophrenia and Depression, NIHM	Veterans Affairs	Guy's and St Thomas' Charitable Foundation, NCCHTA, National Alliance for Research on Schizophrenia 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 pace-maker 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 antipsychotics, 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
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

[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]**
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)
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

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]**
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
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
Transient cognitive impairment	N/A	0 vs 1 (7)	N/A	*UKU scores*[5] *at 3 mo:* 0 vs 0	N/A	N/A

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

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]**
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

[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 anti-depressant 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 ≥ 2 antidepressant trials, score ≥ 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 ≥ 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
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.

Study characteristics						
Author, year, reference number	**Avery, 2006 [64]**	**Su, 2005 [53]**	**Holtzheimer, 2004 [57]**	**Mosimann, 2004 [55]**	**Fitzgerald, 2003 [56]**	**Hoppner, 2003 [95]**
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)
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 antidepressants (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

Study characteristics						
Author, year, reference number	**Avery, 2006 [64]**	**Su, 2005 [53]**	**Holtzheimer, 2004 [57]**	**Mosimann, 2004 [55]**	**Fitzgerald, 2003 [56]**	**Hoppner, 2003 [95]**
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
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

[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]**
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 psychopharmacological 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.

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]**
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
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 contraceptive, 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

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]**
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
Previous therapy	≥2 failed trials of antidepressants (incl. venlafaxine, mirtazapine, valproic, etc.)	≥2 failed trials of antidepressants (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

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]**
***Safety**, n pts (%) (active vs sham)*						
SADEs						
Seizure	N/A	0 vs 0	N/A	N/A	0 vs 0	0 vs 0
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.
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.

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]**
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
Previous therapy	≥ 2 trials of antidepressants	Number of anti-depressant 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)

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]**
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)
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

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]**
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
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 A-7: 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 A-9: 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
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

[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.

[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.

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			
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

Applicability tables

Table A-10: 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 [11], 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 [4, 24].
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 [11], RAZCP [24], CME [4]*

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

[18] Outcome assessors' blinding unclear.

Appendix 2:
Regulatory and reimbursement status

Table A-11: 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 anti-depressant 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 anti-depressant 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 anti-depressant 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), ✪ 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)	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)
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, antidepressant 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							
Europe	Notified Body 0535	Yes	N/A	N/A	2013	Yes	CE577342
USA	FDA	No	N/A	N/A	N/A	N/A	N/A
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 *[33, 35, 39, 96-101]*

Table A-12: 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, the German Association for Psychiatry, Psychotherapy, and Psychosomatics (DGPPN) issued multi-disciplinary, evidence-based guidelines on the treatment of depression [21]. 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 [22].
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 in health institutions only. Indication: Depression – moderate and severe episodes Stimulation of left DLPFC (20 Hz; 2 sec train, 40 pulses, pause 28sec; 40 repetitions = 1600 pulses). Stimulation of right DLPFC (1 Hz – excitation; 1600 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 [41].
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: *[21, 22, 41]*

Table A-13: 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.
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.
Spain	AVALIA-t	rTMS as an add-on therapy is currently not recommended.	There is uncertainty in its clinical efficacy.
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.

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: *[21, 22, 73, 102]*

Appendix 3: Checklist for potential ethical, organizational 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, it 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 [103].	
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 [104]

Appendix 5: Safety guidelines

Table A3: Maximum Safe Duration of Single Trains of 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]Duration per second.
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]

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