Report

Background report on assessing established medical science and medical practice in repetitive transcranial magnetic stimulation (rTMS) in depression

ICD-10 codes:
F32 depressive episode
F33 recurrent depressive disorder

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Summary

The existing literature provides insufficient data to be able to decide whether there is a place for rTMS in the standard of care of depression. There are a lot of well-designed efficacy studies that compare the effect of rTMS on depression with sham-stimulation. However, they often use different stimulation parameters and localisation, which makes it difficult to draw an unequivocal conclusion. The studies usually have a short follow-up. Though favourable effects clearly do exist, there is no standard with regard to optimum technical application. Further systematic research will have to show whether rTMS deserves a place in depression treatment, whatis the best way to deliver it and for which categories of patients with depression there is a reasonable indication.

Currently the use of rTMS for depression does not comply with established medical science and medical practice.

1. Report design

Following a general introduction to the subject of depression, with section 2 providing a short description of rTMS, sections 3 and 4 provide a report of the literature search, the choices involved and a systematic review of results with rTMS in comparison with a non-active treatment (sham-stimulation). Section 5 discusses these results in more detail. Subsequently, section 6 discusses a number of important non-systematic reviews and foreign positions. Section 7 provides a general summarising discussion. Section 8 contains the comments of external experts who were consulted. Lastly, the report also contains sections 9, 10 and 11: the final conclusion, medical-scientific abbreviations used and the literature list.

limitation

The report is limited to research into the effect of rTMS in comparison with a non-active treatment.
Direct comparisons with ECT and antidepressants were not taken into consideration. An examination of the extremely comprehensive literature, by way of familiarisation, revealed that research has been done mainly into the question of whether rTMS has any effect on depression. In fact, the technique is still largely at the phase II stage.

2. Introduction

2.a. Reason

In response to a dispute between an insured client and a health insurer about the reimbursement of rTMS treatment for depression that was obtained abroad, the Health Insurance Complaints and Disputes Foundation (SKGZ) asked CVZ whether this treatment does or does not comply with established medical science and medical practice.

2.b. Background information on depression

The medical concept of depression describes a widespread disorder, the severest cases of which are invalidating and often difficult to treat. The English language literature refers to it as "major depressive disorder" (MDD). From Fitzgerald 2001[1], we learn the following. Depression can become evident in a range of symptoms, such as altered mood, loss of interest in daily activities, lack of activity, disturbed concentration, appetite and sleeping pattern.
About 15% of the population has suffers from depression at least once in their lifetime, or more frequently. This is linked to considerable morbidity and mortality. Clearly it has a great impact on the individual patient, the use of health care facilities and on society.

Pathophysiology

The cause of depression is unknown. The occurrence of symptoms under certain circumstances and the efficacy of psychotherapy give rise to the conjecture that there is a connection with a person's mental and social life. The efficacy of antidepressants and of ECT also lead to the conjecture that there is a connection between the development of the symptoms and physical and chemical aspects of the working of the brain.
There are indications that an imbalance between the left anterior cerebral cortex and the right anterior cerebral cortex plays a role in depression and that anterior stimulation of the left side, or anterior attenuation of the right side can be effective in treating depression[1].

Standard Treatments

There is a whole range of products and methods that are recognised as having a place in the treatment of depression, including numerous antidepressants, psychotherapies and electroshock treatment (electroconvulsive therapy, ECT).
In recent years further improvements have been made in these treatments: the development of a variety of new antidepressants, the implementation of psychotherapies and ECT applications that have become increasingly specific. Nevertheless, treatment fails in a substantial percentage of patients. If psychotherapy and medication are unsuccessful, then ECT is the main remaining possibility. The choice from

various treatment modes is also often limited by the preference or abhorrence of patients for one of the possible methods of treatment. In this respect, see the Dutch multidisciplinary guideline[2].

(New) rTMS intervention

Repetitive transcranial magnetic stimulation (rTMS) is a method for affecting the working of certain parts of the cerebral cortex by generating (via magnetic fields) pulses within it, without the necessity of invasive surgery or applying excessive voltages to the brain.
An electrical pulse is generated in a ring-shaped conductor, above the part of the cerebral cortex being treated, outside the skull and without direct contact with the skull, so powerful that it results in a strong magnetic field being turned on and off rapidly. This induces short-term currents in the cerebral cortex.

In practice takes this means that a patient receives a number of series of TMS pulses above certain areas of the brain during a number of sessions. High-frequency rTMS (usually 10 or 20 Hz, sometimes 5 Hz) increases the excitability of the cerebral cortex and is administered to the anterior left side in cases of depression. In that case, in a given session, 5-20 Hz stimulation is given 20 to 30 times sequentially during a few seconds.
Low frequency rTMS is also used, mostly around 1 Hz. Low frequency is supposed to have an attenuating effect on the cerebral cortex and is therefore mostly used anterior, right side, for depression. This low frequency rTMS is administered in uninterrupted series lasting 15 to 20 minutes.
Each patient receives a number of sessions, varying from at least 5 sessions to daily sessions over 9 weeks.

2.c. Question addressed in the literature study

Question

What is known about the effects of rTMS on depression?
Is the use of rTMS on depression in accordance with established medical science and medical practice?

Patient population

Patients with severe depression: major depressive disorder, MDD).

Relevant outcome parameters

The Hamilton Rating Scale for Depression (HRSD)/Hamilton Depression Rating Scale (HDRS)/HAM-D. This is an "observer-rated" score-list that indicates the severity of the depression, based on the symptoms that occur during the depression, varying from 17 to 28 items that are scored on a 4-point scale.
The Montgomery-Åsberg Depression Rating Scale (MADRS). This "observer-rated" score-list measures the severity of depressive episodes in patients with mood disorders, using 10 items on a 6-point scale.

Required methodological study characteristics	Comparative studies are required that are randomised and sufficiently blind, or meta-analyses of the pooled results of studies that fulfil these requirements. This is particularly important due to the subjectivity of the outcome parameters used for depression.
Comparison	This report is limited to a comparison of active rTMS with a placebo treatment. The latter was almost exclusively "sham-stimulation". This is because an explorative study of the extremely comprehensive literature revealed that research had been carried out mainly into the question of whether rTMS has an anti-depressive effect. In fact, the technique is largely still in the phase II stage. Too little research has been done comparing rTMS directly with the usual treatments for depression to be able to draw a conclusion over its clinical efficacy.

3. Search strategy & selection of suitable studies

Search terms	**Effects of rTMS on depression** Search date:14-02-2011 Case no.: 2011004309
	Medline (PubMed) repetitive transcranial magnetic stimulation OR rTMS OR TMS AND Depression. Filters: in process, meta-analyses, RCTs

Databases and websites consulted

Bibliographic databases	Medline (PubMed) Cochrane library (Wiley) Clinical evidence HTA Databases TRIP-database UptoDate Google Scholar
Websites of government organisations	CKS (UK) CTAF (CA) G-BA (D) HAS (F) HTAi-Vortal INHATA IQWIG (D) KCE (B) LBI (A) MAS (CA) NHS evidence (UK)
Insurers' websites	AETNA ANTHEM Medicaid (CMS) CIGNA Regence Group
Guidelines and systematic reviews	ASERNIP-S Gezondheidsraad National Guideline Clearinghouse NICE

4. Results

4.a. Results of the literature search

Medline

The search in Medline, via Pubmed, supplied in-process (= as yet not indexed in Mesh-terms) articles, 157 RCTs and 15 meta-analyses.
An initial elimination according to relevance to the subject of this report, based on titles and abstracts, left us with 24 in-process articles, 11 meta-analyses and 54 RCTs (all abstracts are attached to this report as a separate appendix: doc. no 2011019382). Five of the meta-analyses focused on the research question addressed in this report. These are summarised briefly in table 1 (of this section) and will be discussed in more detail.
There were also a few RCTs that were too recent to be incorporated into the meta-analyses included. Those that complied with the requirement double-blind and sham-controlled are included in table 2 (of this section) and are discussed separately.
Almost all the RCTs that complied with the requirements were included in the meta-analyses.
The RCTs were assessed independently by two assessors, after which a unanimous assessment was reached.

Other sources Standpoints

In addition, a number of non-systematic reviews were identified from the other sources. Many of the non-systematic reviews were drawn up for the benefit of standpoints over the place of rTMS in insurance packages.
The relevant conclusions are summarised briefly in table 3 (of this section) and discussed in more detail in section 6.

4.b. Tables: meta-analyses, RCTs and reviews/standpoints

Table 1. Summary of the selected meta-analyses

First author, Year of publication	Type Study, follow-up duration	Number of patients	Interventions and comparative treatment	Indication	Relevant outcome indicators	Results	Comments[1]	Risk of bias[2]	Level of evidence[3]
Couturier 2004[3]	Meta-analysis of 6 sham-controlled studies, FU not indicated	Varying from 6 to 30 Total 91	Fast freq. (10-20Hz) rTMS left DFPLC	MDD, bipolar depression	HAMD 21	No significant difference (WMD)	Small studies, therefore insufficient power.	not clear	A1
Schutter 2009[4]	Meta-analysis of 30 sham-controlled studies, FU not indicated	Varying from 2 to 143 Total 1164	Fast freq. rTMS >5 Hz, left DFPLC	MDD	HAMD 21	Combined Effect size 0.39 (clin. relevance not clear)	Combined Effect size comparable with some antidepressants Sham-conditions and blinding not 'waterproof'	Not clear to low	A1

[1] Including comments on assessment of quality of the study, in particular of non-comparative studies.

[2] Determined on the basis of questionnaire/tables (series no. 2010019636). Risk of distorted results: high, low, unclear.

[3] As defined in the report "Assessment of established medical science and medical practice" (series no. 27071300):
A1: systematic review of at least two A2-level studies carried out independently of one another;
A2: randomised double-blind comparative clinical study of a good quality and sufficiently large size (RCT);
B : comparative study, but does not have all A2 characteristics;
C : non-comparative study;
D : expert's opinion.
This classification applies to therapeutic interventions. The evidence must have undergone peer-reviewed publication, irrespective of its level.

First author, Year of publication	Type Study, follow-up duration	Number of patients	Interventions and comparative treatment	Indication	Relevant outcome indicators	Results	Comments	Risk of bias	Level of evidence
Lam 2008[5]	24 sham-controlled studies, FU for 8 studies 1-9 weeks	10-301 total 1092	rTMS left-side for 40 studies, bilateral DLFPC	TRD	HDRS	Risk difference 17%, NNT 6, active: response 25%, sham 17% Remission active: 9%, sham 6%	Non-homogenous group due to varying definition of TRD. Significant effect of rTMS, but the low response and remission rates and the short follow-up do not permit a conclusion of the clinical relevance of the effects	Not clear to low	A1
Slotema[6] 2009	of 34 sham-controlled studies, FU not indicated	Total 1383 pat. (751 rTMS and 632 sham.	rTMS different frequencies. left DLFPC, in 6 studies (also) right. Left with frequencies 5-20 Hz, right 6 or 1 Hz.	Depression	Not stated	Significant difference due to rTMS: weighted effect size 0.55 (clin. relevance not clear)	An important confounder is that, in a large number of studies, the rTMS was started alongside or even simultaneously with antidepressants. Large variation in stimulation parameters. FU and outcome parameters unknown.	Not clear to low	A1
Schutter[7] 2010	9 double-blind sham-controlled studies	Total 252 patients	rTMS low-frequency (<or= 1 Hz), left or right PFC or vertex.	MDD	HAMD 21, HAMD 17, MADRS	Combined effect size 0.63 95%, CI 0.03-1.24 (clin. relevance not clear)	Low freq. rTMS seems more effective than sham stimulation. Effect sizes comparable with the effects of high-frequency rTMS	Not clear to low	A1

Table 2. Summary of the selected RCTs that were not incorporated into the selected meta-analyses

First author, Year of publication	Type Study, follow-up duration	Number of patients	Interventions and comparative treatment	Indication	Relevant outcome indicators	Results	Comments[4]	Risk of bias[5]	Level of evidence[6]
Triggs 2010[8]	Prospective, randomised, sham-controlled, double-blind, parallel group study, 3 months	48	rTMS 5 Hz vs sham (simulation …), left or right prefrontal	MRD	HAMD-24	No difference (rTMS and sham) more effective than left	Use of antidepressants continued during study. Left/right difference larger with sham than with rTMS Social intervention may have had a therapeutic effect on all participants	high	A2
Aquirre[9]	RCT (simple-blind), 4 weeks	34	TMS 1 Hz right prefrontal vs sham RMS	MRD	HDRS	no significant difference Age-group >45 yrs scored better	Small study group. Use of antidepressants continued during study. Short follow-up.	not clear	A2
George[10]	Partially prospective, randomised, sham-controlled, double-blind. Phase 2 and 3: selective and open. No FU	190	rTMS 10 Hz left prefrontal vs sham	MDD	HAMD, MADRS	Phase 1: rTMS group better than shm.	No other treatment with antidepressants shortly before and during study. No follow-up.	Low (phase1) High (phase 2 and 3)	A2

[4] Including comments on assessment of quality of the study, in particular of non-comparative studies.

[5] Determined on the basis of questionnaire/tables (series no. 2010019636). Risk of distorted results: high, low, unclear.

[6] As defined in the report "Assessment of established medical science and medical practice" (series no. 27071300):
A1: systematic review of at least two A2 level studies carried out independently of one another;
A2: randomised double-blind comparative clinical study of a good quality and sufficiently large size (RCT);
B : comparative study, but does not have all A2 characteristics;
C : none-comparative study;
D : expert's opinion.
This classification applies to therapeutic interventions. The evidence must have undergone peer-reviewed publication, irrespective of the level.

Table 3. Summary of reviews for the benefit of standpoints

Organisation or authors, year of publication	Summary of content	Conclusion or standpoint	Any comments.
Health Council of the Netherlands 2008	Short general introduction on application for depression: the Schutter meta-analysis and one large RCT	Recommendations: appropriateness still to be established, guidelines still to be developed. Not to be introduced outside research environment	
AETNA 2011	Short description of the technique, followed by a compilation of summaries of all relevant RCTs, reviews and standpoints	No right to rTMS for any indication whatsoever, including major depression, because its value and efficacy has not been established. "experimental and investigational"	
Cigna[11]	Compilation of summaries of the most recent trials, and of meta-analyses and systematic reviews since 2001.	"Experimental" for every indication, including depression. "Investigational or unproven"	
Regence group[12]	Based on the existing meta-analyses, reviews and RTCs. Older studies also included.	There is insufficient evidence that rTMS is effective on depression; the small size of the groups studied, the short follow-up periods and the significant drop-out percentages undermine the validity of the conclusions.	A conspicuously negative assessment in the light of the other reviews and the conclusions of other reviews.

Organisation or authors, year of publication	Summary of content	Conclusion or standpoint	Any comments.
Nice[13] 2007	Guidance based on a literature "overview"[14] of the material available up to 2007, with extensive description.	Application must be limited to studies that contribute to [answering] the question of how effective the treatment is, and that can provide an answer to the question of what are the best stimulation parameters, localisation and duration.	The NICE guideline 90 from October 2009[15] has adopted the conclusion on rTMS without any further update of the material.
TEC 2009[16] (blue cross/blue shield technology evaluation center)	The five (then) most recent meta-analyses and a number of additional RCTs.	Does no fulfil the criteria because the evidence contains too few data about the permanence of the effects after the treatment period, how the effects are in relation to other methods of treatment. No conclusion on the net health gains can as yet be drawn.	
CTAF 2009[17] (California technology assessment forum	Systematic review of RCTs and their own meta-analysis of five RCTs between 2003 and 2008.	Net health gains are unproven. The therapeutic value in comparison with existing alternatives has not been established.	
VATAP 2010[20] (veterans health adm. Techn. Ass. Program)	Four independent reviews, six related reviews and a number of more recent RCTs	The results are inconsistent. The reviews agree in the conclusion that the available evidence does not permit a final conclusion. For the rest, the wide divergence between the interpretations of the evidence serve to emphasise the uncertainties surrounding rTMS	

5. Discussion: meta-analyses and additional RCTs

Meta-analyses

Couturier 2004[3] Couturier (2004)[3] wrote a review of the literature then available. One aspect of this was a meta-analysis of the randomised, sham-controlled studies of rTMS above the left dorsolateral prefrontal cerebral cortex (DKPFC). It involved only six studies, with low numbers of test subjects: varying from 6 to 30, giving a total of 91. The pooled material did not supply a statistically significant improvement in the symptoms. The author did mention that the power of the included studies was low due to the small numbers of test subjects and that larger studies were necessary in order to detect clinically relevant improvements.

Schutter 2009[4] Schutter (2009)[4] compiled a meta-analysis of all randomised, double-blind, sham-controlled studies of rTMS on depression. The thirty studies found were fairly homogenous with respect to the techniques used, localisation and the outcome parameters used. However, there was more heterogeneity with respect to treatment duration, treatment frequency and patient inclusion criteria. The conclusion was that the anti-depressive effects of rTMS on the left DLPFC are greater than those of sham-stimulation. It is difficult to deduce how great the clinical value would be in practice. An indirect comparison with placebo-studies of medicines reveals that rTMS achieves effect sizes that are comparable with some antidepressants, though this does not mean that rTMS is just as effective. This would require a direct comparative study that is properly set up.

Lam 2008[5] The Lam publication[5] is a review including his own meta-analysis of a number of studies. For this he selected 24 sham-controlled studies of patients with a therapy-resistant depression (TRD). However, this large number was at the expense of the homogeneity of the group of patients, as the concept of TRD was defined rather loosely. Although the antidepressant effect was statistically significant, the remission rates were low and the follow-up short, so that this meta-analysis does not sufficiently answer the question of the clinical relevance of the effects.

Slotema 2009[6] The Slotema publication includes a number of meta-analyses of various possible indications for rTMS. With respect to TRD, the conclusion is that, in comparison with sham-stimulation, the weighted effect size in the pooled material shows a significant advantage for rTMS. The meta-analysis comprises an extremely large number of 34 studies, which was at the expense of the homogeneity. Homogeneity did exist with respect to stimulation parameters and groups of patients. The results may also be distorted by the combination with antidepressants or simultaneously starting them.

Schutter 2010[7]

Schutter (2010)[7] published a "quantitative review" of the available trials on the effects of low-frequency rTMS. As a pooled analysis of the results was made, we have classified this study among the meta-analyses. The analysis made use of the nine available double-blind, sham-controlled studies. In four of the nine studies rTMS was used above the right prefrontal cortex, in the others bilaterally, above the vertex or above the left frontal cerebral cortex. Although the analysis shows that this form of rTMS did have an effect, it is not clear whether this effect is sufficient to be regarded as clinically relevant.

Additional RCTs

3 recent RCTs

Three more recent RCTs which fulfilled the inclusion criteria were found. These were published after the meta-analyses we discussed. We looked at whether the outcomes of these studies are important for the final conclusion. The characteristics and the outcomes are presented in table 2 (section 4). Triggs (2010)[8] and Aquirre (2010)[9] did not supply any significant results; both studies had a certain risk of bias due to confounding: the treatment was concurrent with treatment with medicinal antidepressant treatment or social interventions. George (2010)[10] did a trial with a complex set-up, the first three-week phase of which was a randomised, double-blind study. In this phase there was a statistically significant advantage with respect to number of remitters in the rTMS arm. After the three weeks came phases two and three, without blinding, and with selected assignment based on the results from phase 1, which inevitably involved a considerable risk of distortion.
All in all, this means that the new material carries little added weight.

6. Discussion: reviews and positions from elsewhere

Fitzgerald 2011

The most recent review is that of Fitzgerald and Daskalakis[1], which provides an extremely extensive summary of the state of affairs. The review is partly based on effectiveness studies and meta-analyses that were published up to and including 2010. It is not a systematic review. In brief, the authors point out the fact that the search for the optimum administration technique and localisation is an on-going one. There are still only preliminary studies on some of the newer forms for administering rTMS. Their contribution also shows that the development of rTMS for the treatment of depression coincides with the attention being given to related techniques such as direct transcranial electrostimulation, deep brain stimulation (DBS), direct cortical stimulation and magnetic stimulation with weak magnetic fields. Finally, they conclude, with respect to efficacy, that although it has been established that rTMS does have a certain therapeutic effect on depression, its size is still uncertain and whether, in the end, it is sufficiently clinically relevant. In view of the current trials and developments, they expect to have more clarity about all the above-mentioned aspects within five years.

Literature studies

Table 2 (section 4) provides a short systematic review of the many literature studies that have been done on behalf of standpoints and guidelines abroad. These are all based on a compilation of the available literature. The conclusions are always, though with some slight differences, that despite the fairly established antidepressant effect, there are still too many uncertainties to be able to give rTMS a place in rights or guidelines. A guideline has been published in Canada[18] that awards it a place where previous treatment has failed ("second line treatment"). The following is a short discussion of the two most informative and perspicuous standpoints.

Aetna 2011

Recently, in 2011, Aetna[19] carried out a thorough screening of the peer-reviewed literature from 2003 up to and including 2009 for reviews, meta-analyses and trials involving rTMS for psychiatric use. They provided a short description of the content, conclusion and quality of all the articles found. With respect to depression, Aetna concluded – albeit without a systematic analysis of the collated material – that the influence of the different stimulation parameters used had not been properly investigated, that the effectiveness had been insufficiently established and that almost nothing had been published on long-term results.

Flynn 2010

On behalf of the Technology Assessment Program (TAP) of the Veterans Health Administration (VA), Flynn et al. [20] wrote a critical short summary, based on the existing reviews on rTMS

up to the end of 2008, whereby they stipulated strict requirements of the material on which these reviews were based and on the method used in the reviews to analyse the material and the arguments for the conclusions. In the end, they included ten independent reviews, four of which were devoted to rTMS for depression. They ascertained that these agreed in the conclusion, that the research results were inconsistent and that it was not possible to form a solid conclusion on its effectiveness.

7. Summarising discussion and conclusions

General background

In 2008, within the context of an "early warning", the Health Council of the Netherlands (*Gezondheidsraad, GR*) issued a statement on rTMS[21]. The treatment was already on commercial offer. According to the GR, favourable effects were particularly noticeable in people who suffer from a depression that is immune to medication, but broader research was still necessary into its effectiveness and guidelines should be developed.
Almost three years have now gone by. The most recent elaborate review of this subject is the above-mentioned review of Fitzgerald and Daskalakis[1]. They conclude that compared to sham-stimulation, rTMS is the more effective. The most-used method is high-frequency left-frontal treatment, but there is also said to be a place for low-frequency right-frontal treatment. Further research should go into bilateral use and alternative methods for optimum localisation of the cortex being treated.

The meta-analyses, RCTs and reviews included in this report clearly show that there are still many variations in the method of use. Due to the nature of the matter, the lack of a technical standard treatment makes it difficult to evaluate optimally the place rTMS could or should have in the treatment of depression. There are many variations in use:

- locality, and determining the optimum location
- optimum Hz-frequency (in conjunction with the chosen location for stimulation)
- the frequency of administering series, number per session, number of sessions, etc.

Although the meta-analyses are based on a critical choice of initial material, a number of aspects could affect the validity: most authors do not regard blinding via sham-stimulation as 100% watertight; there is generally little homogeneity with respect to the stimulation parameters and treatment frequency and most of the studies often have small and differing study populations.
The meta-analyses differ in the inclusion criteria of articles on which they are based. Nevertheless, as far as the included studies are concerned, there is a large overlap between the meta-analyses, because they were published shortly after one another and do demonstrate considerable similarities in the inclusion criteria. They are, therefore, not independent of one another.

Conclusions

The following can be concluded on the basis of the available evidence:
1. It has been fairly well established that rTMS can have a therapeutic effect on depression.

2. It is still insufficiently clear as to the group of patients on which rTMS is effective.
3. Whether that effect is clinically relevant and lasts long enough to give the treatment a permanent place in our standard of care has not been established.
4. The optimum stimulation parameters, treatment frequency and duration of treatment still have to be established.

Roughly speaking, these conclusions agree with what can be found in foreign guidelines and position papers.
In view of the direction in which the evidence is pointing, and the prospects of being able to improve standardisation of the treatment and the indication, it may be necessary to re-evaluate the issue within a few years.

8. Consultation regarding contents

Experts

The executive board of the Dutch Association for Psychiatry, the NVvP, sent a draft version of this background report to Dr. Odile A. van den Heuvel, Psychiatrist at the VU Medical Centre. She did not find any lacunas in this report. She provided the following account of the draft report.

Expert account

Based on current established medical science, the conclusion can be drawn that using rTMS is evidently valuable for experimental research, as it can provide insight, partly via combined use with diagnostic brain research, into the underlying neural mechanisms of psychiatric disorders, including depression. On the other hand, use of this non-invasive technique in modulating brain activity requires more research with regard to its clinical application. In spite of the fact that rTMS clearly seems to have an antidepressant effect, insufficient comparative research is done into the multiplicity of stimulation and treatment parameters (location of stimulation, frequency of stimulation pulse, frequency of rTMS sessions, number of pulses/session, number of rTMS sessions/treatment, % MEP, etc.), so it is still not possible to issue clear advice on TMS as a standard method of treatment of depression and which stimulation parameters should be used.

Research necessary

I feel that research into the above-mentioned subjects should, within a relatively short period of time (a few years), provide improved insight into the efficacy of rTMS and more explicit advice regarding its place in the treatment guideline.

(1) Distinguish between (a) rTMS as standard treatment of depression (1st or 2nd step in the protocol instead of psychotherapy or medication); (b) rTMS as monotherapy for therapy-resistant depression, or (c) rTMS as adjuvant therapy alongside psychotherapy or medication for therapy-resistant depression.
N.B. Little is currently known about a possible interaction between rTMS and medication, though it is to be expected in view of the effect of rTMS on the neurotransmitter systems. One might even expect a contra-effect, depending on whether a patient did or did not use medicine during the rTMS treatment phase.

(2) Stimulation parameters

- location + lateralisation on the skull, using (a) number of centimetres from the primary motor cortex, (b) structural scan of the patient, (c) functional scan session of the patient. The present conclusion is that preference goes out to high-frequency stimulation of the left dorsolateral prefrontal cortex. A study of Sack et al. (2008) shows that

the specific part of the prefrontal cortex can be stimulated most accurately using neuro-navigation based on an individual functional MRI scan.
- pulse frequency
- number of pulses/session
- session frequency
- number of sessions
- % MEP
- other stimulation uses, such as theta-burst stimulation (TBS)

(3) what should be done once rTMS treatment has ceased? Maintenance treatment with rTMS? Different follow up with medication or psychotherapy?
(4) Study of long-term effects: How long does the treatment effect last, and what is the chance of a relapse in comparison with other treatment forms?

(5) Study of favourable and unfavourable side effects in the long term, such as the structure and function of the brain. Medical brain imaging shows that rTMS leads to an immediate alteration in neurotransmitter release and brain activation. What are the long-term structural and functional effects? How reversible are these effects? And what are the consequences of a contra-effect (e.g., inhibition of a part of the brain instead of the intended stimulation)?

(6) Further research into promising technological developments: e.g., theta-burse stimulation (TBS): Shorter stimulation (large advantages re ease of use) for longer-lasting effects.
(7) Study into specific indications for treatment: What are the patient characteristics for a positive response (e.g., age, co-morbidities, etc.)?
(8) comparative study of rTMS versus other treatment forms, with direct comparison of effect sizes.

Limitation of research method

The study into the efficacy of rTMS is particularly hampered by the lack of a good placebo condition. The placebo coil clearly leads to a different sensation that the real coil, whilst stimulation of a so-called non-effective location (e.g., the vermix) can result in a therapeutic effect via transsynaptic connections with a brain circuit that is relevant to depression. The first could lead to an artificially high effect size, whilst the second could lead to an inaccurately low effect size.

implementers

A separate matter from the efficacy of rTMS as treatment for depression, is the competence of those who carry out the treatment, which has not yet – to my knowledge – been described with sufficient clarity. Though the prescription of medicine is the domain of physicians and cognitive behavioural therapy clearly demands psychotherapeutic training, few criteria have been stipulated that care-providers must fulfil in order to be able to assess inclusion and exclusion criteria for determining an indication for treatment and to be capable of implementing the treatment and coping with possible side effects (including an epileptic attack). Whilst for electroconvulsive therapy there is a national work-group that works on bundling knowledge and safeguarding the quality of this treatment form, the organisation of TMS in the Netherlands is more diffuse. A national TMS work-group could also bundle knowledge and guarantee research, which may increase the speed with which clarity is provided over the place that TMS can take in the guidelines on treatment for depression."

These are the comments of the expert.

9. Position regarding established medical science and medical practice

The treatment of depression with rTMS does not fulfil the criterion "established medical science and medical practice".

10. Medical-scientific abbreviations used

DLPFC = dorsolateral prefrontal cortex

ECT = electroconvulsive therapy

HRSD = Hamilton rating scale for depression

HDRS = Hamilton depression rating scale

MEP = motor evoked potential

MDD = major depressive disease

PFC = prefrontal cortex

rTMS = repetitive transcranial magnetic stimulation

TRD = therapy-resistant depression

TBS = thèta burst stimulation

11. Literature list

[1] Fitzgerald PB and Daskalakis ZJ. The effects of repetitive transcranial magnetic stimulation in the treatment of depression. Expert Rev Med Devices 2011; 8: 85-95.
[2] CBO, multidisciplinary guideline on Depression, 2010 version, consulted May 2011. http://www.cbo.nl/Downloads/1065/rl_depr_update_10.pdf
[3] Couturier JL. Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: a systematic review and meta-analysis. J Psychiatry Neurosci 2005; 30: 83-90.
[4]Schutter DJLG. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol Med 2009; 39: 65-75.
[5] Lam RW, Chan P, Wilkins-Ho M, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. Can J Psychiatry 2008; 53: 621-31.
[6] Slotema CW, Blom JD, Hoek HW, et al. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry 2010; 71: 873-84.
[7] Schutter DJLG. Quantitative review of the efficacy of slow-frequency magnetic brain stimulation in major depressive disorder. Psychol Med 2010; 40: 1789-95.
[8] Triggs WJ, Ricciuti N, Ward HE, et al. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: a randomized, sham-controlled trial. Psychiatry Res 2010; 178: 467-74.
[9] Aguirre I, Carretero B, Ibarra O, et al. Age predicts low-frequency transcranial magnetic stimulation efficacy in major depression. J Affect Disord 2010; aheadofprint: nov, 17.
[10] George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 2010; 67: 507-16.
[11] **CIGNA.** Transcranial Magnetic Stimulation. 2011. Consulted in February 2011 via http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0383_coveragepositioncriteria_transcranial_magnetic_stimulation.pdf
[12] **Regence Group**. Transcranial Magnetic Stimulation as a Treatment of Depression and Other Psychiatric/Neurologic Disorders. 2011. Consulted in February 2011 via http://blue.regence.com/trgmedpol/mentalHealth/mh17.html
[13] **NICE.** Transcranial magnetic stimulation for severe depression. 2007. Consulted in February 2011 via http://www.nice.org.uk/nicemedia/live/11327/38391/38391.pdf
[14] **NICE.** "Interventional procedure overview of transcranial magnetic stimulation for severe depression" (2006), available via http://www.nice.org.uk/nicemedia/live/11327/31723/31723.pdf
[15] **NICE**. Depression in adults. 2009. Consulted in February 2011 via http://www.nice.org.uk/nicemedia/live/12329/45888/45888.pdf.
[16] **Blue Cross Shield**. Transcranial Magnetic Stimulation for Depression. 2009. Consulted in February 2011 via http://www.bcbs.com/blueresources/tec/vols/24/24_05.pdf
[17] **CTAF**. Repetitive Transcranial Magnetic Stimulation for Treatment Resistant Depression. 2009. Consulted in February 2011 via http://www.ctaf.org/files/1028_file_rTMS_W.pdf
[18] Kennedy SH, Milev R, Giacobee P, et al. Canadian network for mood and anxiety treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. J Affective Disorders 2009;117:S44-S53.
[19] **AETNA**. Transcranial Magnetic Stimulation and Cranial Electrical Stimulation. 2011. Consulted in February 2011 via http://www.aetna.com/cpb/medical/data/400_499/0469.html.
[20] **VATAP**. Trans-Cranial Magnetic Stimulation For Depression. 2010. Consulted in February 2011 via http://www4.va.gov/VATAP/docs/TMSdepression2010.pdf.

[21] **Gezondheidsraad**. Transcranial magnetic stimulation in psychiatry and neurology. Horizon scanning report. 2008. Consulted in February 2011 via http://www.gezondheidsraad.nl/sites/default/files/200821.pdf