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REVIEW ARTICLE

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Effects of Hesel-coil deep transcranial magnetic stimulation for depression – a systematic review

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ABSTRACT

Background: One third of the depressed patients are not improved by antidepressant drugs and psychological treatments, and there is a need for additional treatments. Repetitive transcranial magnetic stimulation (rTMS) is being developed towards an alternative in treatment-resistant depression. Deep transcranial stimulation (dTMS) with the Hesel-coil (H-coil) is a further development of rTMS aiming to enhance the effect by getting the magnetic pulses to penetrate deeper into the brain.

Aims: This report aims to assess the evidence-base for dTMS for depression. The report also includes an assessment of the ethical and economic aspects involved.

Methods: A systematic review of the effects of H-coil dTMS on depression was conducted and the scientific support was evaluated using GRADE (Grading of Recommendations Assessment, Development and Evaluation).

Results: Only one controlled study was identified. In the sham-controlled randomized study, 212 participants with major depression that had not responded to antidepressant medication were enrolled. A two-point superiority in Hamilton Depression Rating Scale was observed in the dTMS arm vs the sham-arm at 4 weeks, but the difference was not statistically significant. No serious adverse events were reported apart from rare cases of epileptic seizures.

Conclusions: The existing scientific support for H-coil dTMS therapy for depression is insufficient. The clinical implication is that the use of dTMS in depression should be restricted to the framework of clinical trials pending further studies. Fortunately, additional studies are underway and the evidence base should presumably improve over the next several years.

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Background

Depression is a common condition (1) that most often either responds to treatment or resolves spontaneously (2). However, if treatment efficacy is not sufficient and the condition becomes long-term or chronic, the burden for both the patient and the patient's environment becomes significant (3).

Antidepressant drugs and psychological treatments are not always sufficient to produce an antidepressant response (4), which warrants second-line treatment strategies. The American STAR*D-study (Sequenced Treatment Alternatives to Relieve Depression) intended to enable an incremental treatment algorithm, primarily with antidepressant drugs. The alternatives included changing to another medication, addition of a different medication, new combinations of medications, and cognitive behavioural therapy (CBT). One third of patients that completed the study did not sufficiently benefit with standard treatment regimens and need alternatives (5).

Electroconvulsive therapy (ECT) was not included in the STAR*D-study, but is a well-established treatment for severe depression. In Sweden – a country with 9.5 million inhabitants – ~4000 patients per year receive ECT (6). With repeated administrations, ECT is highly effective in relieving depressive symptoms: The percentages of patients achieving remission in two recently completed clinical trials was 64% (7) and 60% (8), respectively, although the results may be less favourable in clinical practice (9).

Treatment-resistant depression (TRD) is usually defined as depression that has not responded to adequate treatment with at least two types of antidepressant drugs. ECT may be beneficial in TRD, but the effect is usually less striking than that observed with first-line treatment of severe depression with melancholic and/or psychotic traits (10–13). The later ECT is applied in a sequence of treatment initiatives, the greater the risk of a generally treatment-resistant depression.

The side-effects of ECT include usually transient and limited cognitive impairments. It is uncommon that patients have prolonged memory impairment; in such cases it may be difficult to determine whether depression or ECT caused the memory

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Supplemental data for this article can be accessed here.

impairment. Another drawback of ECT is that the treatment is resource-intensive. ECT is not always effective or suitable and some patients do not wish to receive ECT. There is, hence, an urgent need for additional treatment alternatives.

Repetitive transcranial magnetic stimulation (rTMS) was introduced as such an alternative. In rTMS an electromagnetic coil, usually formed like a figure-8, is placed on the patient's head. This induces weak electrical fields in the cerebral cortex a few centimetres deep that can depolarize groups of nerve cells and trigger action potentials (14). The treatment does not produce convulsions except as a rare side-effect, and there is no need for anaesthesia.

rTMS has been used for treatment of patients with TRD and also as first-line treatment for severe depression. The Swedish Council on Health Technology Assessment (SBU) reviewed the scientific basis for the method in 2009 (15). This review and a later meta-analysis conclude that rTMS has a symptom-alleviating effect on treatment-resistant depression (16,17), but that the method is not as effective as ECT (18). Common side-effects of rTMS include pain at the stimulation site, headache, and dizziness. Generalized epileptic seizures of the grand mal type have been reported but are uncommon. The treatment is not thought to cause memory impairment (15). The use of rTMS is not yet widespread in Sweden as compared to ECT: According to a survey in 2014 by the National Quality Register for ECT, rTMS devices were available at only five Swedish hospitals and ~40 patients received rTMS in 2014.

Deep transcranial stimulation (dTMS) is a further development of the pulsating electromagnetic coil used in rTMS. The objective is to get the magnetic pulses to penetrate deeper into the brain. This requires greater energy and, as a result, the stimulation becomes less focused. Moreover, deeper penetration possibly means increased risk of triggering epileptic seizures (14). Several technical solutions have been proposed to overcome these hurdles. One is referred to as the H-coil (Hesel coil), which is a special winding of the electromagnetic coil that comes in different variations and features.

dTMS treatment with an H-coil and comparison to rTMS

dTMS is similar to other forms of rTMS. The patient is awake during treatment and, during stimulation, loud snapping noises occur that may cause hearing damage. The patient is, therefore, given earplugs. Prior to treatment, the point on the patient's scalp (and consequently the underlying part of the cortex) which the magnetic pulses will be aimed at is plotted. Determining the treatment points involves selection of the hemisphere to be treated and the use of the electromagnetic coil to search the point in the motor cortex that requires the least stimulation intensity to activate the extensor muscle of the thumb on the opposite hand. This intensity is defined as 100% and is referred to as the motor threshold. Treatment strength is then defined in the percentage of the motor threshold, such as 110%. The coil is then placed 6 cm in front of the motor point, over the prefrontal cortex, and this then serves as the treatment point (19).

However, dTMS differ from most other forms of rTMS in that the electromagnetic coil is placed in a hood in dTMS. One study evaluated various positions and treatment strengths with the H-coil and found that unilateral stimulation over the left prefrontal cortex with an energy equivalent to 120% of the motor threshold was most effective (19).

Contraindications for dTMS are the same as for other forms of rTMS and include metallic objects in the head or eye, implanted pacemakers or other implants. Relative contraindications include previous epilepsy, skull trauma, severe headache or migraine, hearing loss, substance abuse, pregnancy, and systemic disease.

Each dTMS treatment session includes a series of 2-s stimulations with a frequency of 18–20 Hz followed by a 20-s pause, and requires a total of 15–20 min. One treatment session is thereby the equivalent of 40–55 stimulations, with a total of ~1700–2000 magnetic pulses. Treatment is administered 5 days a week for 4–5 weeks.

Kedzior et al. (20) have summarized the available open studies of dTMS for depression in a meta-analysis. In eight studies (124 patients, 67% on concurrent antidepressant), 20 sessions of dTMS resulted in a 29% remission rate (95% confidence interval = 17–44%). However, it is difficult to draw firm conclusions on the basis of uncontrolled studies. Therefore, there is a need for a systematic review to summarize the scientific basis for the treatment of depression with an H-coil deep transcranial magnetic stimulation.

Aims

The purpose of this report is to respond to the following questions:

Does H-coil dTMS have an effect on depression?

Can H-coil dTMS replace ECT in treatment of depression?

Is H-coil dTMS an alternative for patients with treatment-resistant depression?

What side-effects and complications occur with H-coil dTMS and how common are they?

The report also includes an assessment of the ethical and economic aspects involved.

Methods

A systematic review of the effects of H-coil dTMS on depression was conducted and the scientific support was evaluated using GRADE (Grading of Recommendations Assessment, Development and Evaluation) (21).

Eligibility criteria (PICO) were:

Population: individuals with major depression or bipolar depression according to DSM or ICD classifications.

Intervention: H-coil dTMS.

Comparison: another treatment or placebo (sham) or different doses of H-coil dTMS.

Outcome: response, remission, or score reduction on a validated depression scale.

Other: controlled studies with- or without randomization published in English, German, French, or a Scandinavian language.

Search strategy

Pubmed, Cochrane library, Embase, and PsycInfo were searched in November 2014, combining synonyms for

transcranial magnetic stimulation and depression. Reference lists of included and excluded studies and reviews were searched for additional references. Two authors independently screened titles and abstracts. The detailed search criteria are available in the Online Appendix.

Assessment of bias

Bias was assessed using the SBU checklist, including the following items: randomization, allocation, blinding (of participants, doctors, and data collectors), drop-out, and potential conflicts of interest.

Results and discussion

Scientific support for dTMS using an H-coil for depression

As per December 2014, we could not identify any published controlled studies of the effect of dTMS on depression (See Figure 1 and Online Appendix Search strategies). However, we gained access to a manuscript reporting results from a randomized placebo-controlled multi-centre study that was later accepted for publication (22). The purpose of that study was to examine the safety and efficacy of daily H-coil dTMS during 4 weeks followed by continued treatment for up to 12 weeks. Participants were patients with major depression who had not improved after 1–4 treatment attempts with antidepressant drugs. A total of 20 centres in the US, Israel, Germany, and Canada participated in the study. The patients were between 22–68 years old and suffered from depression that fulfilled the DSM-IV criteria for a major depressive episode of the first or recurrent type. These episodes had continued for periods ranging from 1 month to 7 years. Symptom severity was equivalent to a score of at least 20 on the Hamilton Depression Rating Scale with 21 questions (HAMD-21). Any antidepressant medications were discontinued before the trial was begun. Just over 900 patients were screened through advertisement or doctor referral. After a preliminary telephone assessment followed by clinical examination, 212 patients remained. These were used in the intention to treat (ITT) analysis. Of these, 31 who did not meet the criteria for adequate treatment were excluded.

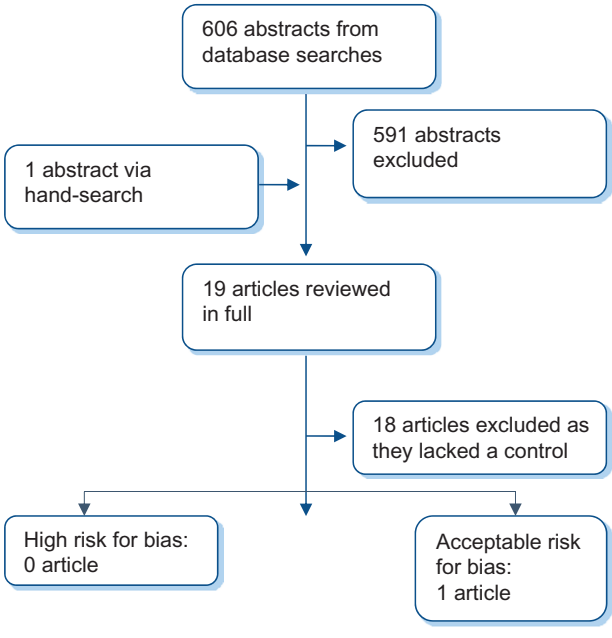

Figure 1. Flow chart of literature review and selection of studies.

Treatment was administered 5 days a week for 4 weeks, followed by twice-weekly treatment for up to 12 weeks. The treatment target was the dorsolateral prefrontal cortex on the left side with an intensity of 120% of the motor threshold with 2-s stimulations with 18 Hz followed by a 20-s pause, repeated 55 times over a total of ~20 min. The study utilized an ambitious system for blinding. A placebo coil was placed next to the H1-coil and the coil was selected for each patient with a pre-programed card that was placed in a card reader attached to both-coils. Sham treatment was, thereby, carried out in the same way as active treatment.

The primary outcome variable was score change on the HAMD 21 after 4 weeks, i.e. before maintenance treatment started. The treatment-group scored 2.3 points lower than the placebo group, but the difference was not statistically significant (Table 1). Secondary outcome measures were halving of HAMD 21 score (response) and score less than 10 points (remission), see Table 1.

Only 43 patients in the treatment group and 28 patients in the sham treatment group completed 16 weeks of treatment. Of these, 41% and 29%, respectively, achieved remission, but the difference was not statistically significant.

The most common side-effects reported in the published article were headache (26.7% in the group having received dTMS with H-coil and 18.9% in the sham treatment group) and pain at the stimulation site (5% with H-coil dTMS and 0% with the sham treatment; a statistically significant difference). One patient suffered a generalized seizure in conjunction with a dTMS session with H-coil.

In addition, there were side-effects during the trial that were reported to the FDA, but that were not reported in the article (http://www.accessdata.fda.gov/cdrh_docs/pdf12/k122288.pdf): Jaw pain (10.2% vs 0.8%), application site pain (25.0% vs 0.8%), and application site discomfort (19.4% vs 4.1%) were statistically significantly more common in the dTMS group as compared to the sham-group.

The project group determined the strength of the scientific support for efficacy on patients with treatment-resistant depression after 4 weeks using GRADE (Grading of Recommendations Assessment, Development and Evaluation) (21). Given that there is only one controlled study, the scientific support was deemed insufficient. Further observations were that the study included patients recruited through advertisement and that it is unclear how the population differs from psychiatric patients. The difference in outcome was not statistically significant in the 'intention to treat' analysis on the primary end-point. The study was financed by the company that supplies the product, meaning that it is not possible to eliminate risk of conflicts of interest and reporting bias. Finally, treatment outcome was compared with sham treatment with an inactive coil, which is valuable as an initial step to evaluate the method. In order to determine whether the effect is clinically relevant,

however, studies comparing H-coil dTMS with established treatment alternatives are required.

dTMS as replacement for ECT

No clinical trials have compared dTMS to ECT in the treatment of depression. Moreover, no comparative clinical trials have investigated if dTMS is effective in severe depression for hospitalized patients, the main indication for ECT. Considering that ECT is highly effective in this indication, dTMS cannot currently replace ECT.

dTMS for pharmacotherapy resistant patients

The Levkovitz et al. (22) study indicates that dTMS could have some effect on moderately depressed outpatients that have not benefitted from prior pharmacotherapy. These patients tend to have relatively low remission rates with current standard treatments (4), and the benefit from ECT is less striking in this patient category than for severely depressed melancholic patients (10–13). These differences in treatment responses might suggest different pathophysiological mechanisms. If future studies show that dTMS is more effective or better tolerated than available treatments for moderately depressed pharmacotherapy-resistant outpatients, dTMS might fill an important treatment gap. However, this hypothesis needs to be tested in clinical trials that compare dTMS with other treatments, such as ECT, before dTMS can be used outside the framework of clinical studies.

Ongoing studies of dTMS

Four ongoing randomized studies of H-coil dTMS and unipolar depression were identified in the database www.clinicaltrials.gov. For one of these the information has not been updated since 2011 (effect of combining H-coil dTMS and SSRI) and it is unclear how the study has progressed. Three other studies are recruiting patients. One post-marketing study aims to recruit 80 patients and is using an inactive coil as a control. Another study is comparing two different stimulation frequencies for H-coil dTMS and the third is comparing H-coil dTMS with rTMS with another coil. All studies are carried out in collaboration with the company that developed the method and are relatively small.

A research group at the Karolinska University Hospital in Sweden is planning two randomized studies. In one of these, three different doses of H-coil dTMS will be compared. In the other study, the method shall be compared with ECT. The latter of these studies is intended to examine the treatment outcomes including effects on memory. The study is expected to take 2 years.

Economic aspects

Evaluating the cost-effectiveness of dTMS compared with ECT requires knowledge of the differences in effect and side-effects between the methods, but there is currently insufficient data to make the comparison. On the other hand, it is possible to estimate the costs for treatment with the two different methods.

Table 1. Effects of H-coil dTMS on treatment-resistant depression (22).

Reference country study design	Care environment population	Intervention participants follow-up time drop-out	Control participants follow-up time drop-out	Effect, the study's primary outcome measure (95% CI)	Effect, secondary outcome measure
Levkovitz et al. (22) 2015 Multinational RCT	*Care environment*: 20 hospitals in the US, Canada, Germany, and Israel *Population*: $n > 900$ with DSM-IV diagnosis of major depression screened through advertisement and referrals $n = 212$ fulfilled inclusion criteria and consent; *Inclusion criteria*: CGI-S ≥ 4 and HDRS-21 ≥ 20 Failed to respond to 1–4 treatments with antidepressant medications	I = H-coil dTMS $n = 89$ (47.5% women) *Age*: 45.1 ± 11.7 years *Dose*: 2 s impulse, 18 Hz 120% of threshold value, followed by 20 s pause ×55 in each session. *Drop-out*: 4 weeks: 7.9% 16 weeks: 43.8%	C: sham treatment $n = 92$ (47.7% women) *Age*: 47.6 ± 11.6 years Conditions the same as for the intervention group *Drop-out*: 4 weeks: 16.3% 16 weeks: 53.3%	*Change in HDRS score after 4 weeks*: I: −6.17 (−7.78 to −4.55) C: −3.94 (−5.58 to −2.29) $p = 0.0578$	*Percentage of responders after 4 weeks*: I: 37.0% C: 27.8% $p = 0.0310$ *Percentage remission*: I: 30.4% C: 15.8% $p = 0.0158$

Treatment costs depend largely on the number of treatments each piece of equipment will be used for per year, and these are, therefore, presented below for intervals of between 20–200 treatment series per year and device.

One treatment series of ECT includes seven treatment sessions and each treatment takes ~60 min (15 min of treatment and 45 min preparation and post-treatment routines). The equipment needed to perform ECT treatment costs ~€23 200 and has an estimated lifetime of 10 years (personal communication with Hadi Ghane and Per Dahlin, representatives from MECTA and Thymatron, May 2015).

According to the company that markets dTMS in Sweden, a treatment series of dTMS includes 20 treatment sessions, and each treatment takes ~20 min (personal communication via email with Bengt Sundqvist, Brainsway, 2 February 2015). The equipment is made available through a leasing arrangement with an unlimited number of treatments during the leasing period. The price is ~€73 800 for a 1-year contract. The company estimates that the equipment can be used for 10 patient treatments of ~20 min per day.

In addition to the costs for the hardware, there are costs for the personnel to perform the treatment and costs for pharmaceuticals and consumable material. dTMS is usually administered by a nurse, while ECT requires a number of different specialists to be involved (see Table 2). Since ECT requires more personnel than dTMS, the difference in cost decreases between treatments when salaries are factored in. When each device is used for more treatments, the difference in treatment cost is decreased (see Figure 2).

Table 2. Personnel time required in treatment with ECT and dTMS.

	Average time per treatment (min)	
	ECT	dTMS
Physician[a]	15	0
Anaesthesiologist/anaesthesiology nurse	15	0
Psychiatric nurse	15	0
Nurse/nursing assistant	45	20

[a]Physician cost based on average cost for a resident doctor. Source: McLoughlin et al. (23) as well as personal communication by email with Bengt Sundqvist, Brainsway, 2 February 2015 adjusted to Swedish clinical practice.

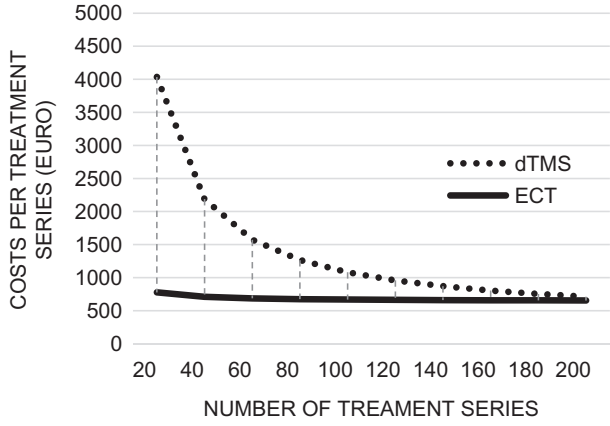

Figure 2. Cost per treatment series (seven treatments for ECT and 20 treatments for dTMS), including personnel time. An exchange rate of 9.48 SEK/EUR was used to calculate the costs.

Ethical aspects

The need for improved treatments for depression is great, but the introduction of new treatments will compete for resources with established effective treatments. Therefore, before new methods are introduced, they must have a well-documented effect. Scientific support for H-coil dTMS is yet insufficient. Prioritizing H-coil dTMS over other treatments considered effective may, hence, lead to an inefficient allocation of resources. Moreover, if dTMS is offered in severe melancholic depression, there is a risk that the chances of remission are reduced as compared to if ECT would have been used. This is an ethical problem considering the need for fast symptomatic improvement to relieve suffering and reduce suicide risk in the patient group.

However, H-coil dTMS is a modern alternative that is attractive to evaluate in clinical trials. If H-coil dTMS in future studies is demonstrated to be effective against depression, then the treatment could be a valuable addition to the treatment arsenal. There is, therefore, an urgent need for more studies of H-coil dTMS, particularly studies comparing H-coil dTMS with other effective treatments.

Conclusion

The scientific support for H-coil dTMS therapy is considered insufficient for depression in non-selected groups as well as for treatment-resistant depression. There are no completed studies comparing H-coil dTMS against other effective treatments. Consequently, we suggest that the use of dTMS should be restricted to the framework of clinical trials pending further studies. Fortunately, additional studies are underway in which H-coil dTMS is compared to ECT and to rTMS with other coil types, and the evidence base should presumably improve over the next several years.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. AN and ML are steering committee members of the Swedish National Quality Register for ECT. AN, BM, and ML are trained in ECT; BM is trained in rTMS.

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References

1. Ellervik C, Kvetny J, Christensen KS, Vestergaard M, Bech P. Prevalence of depression, quality of life and antidepressant treatment in the Danish general suburban population study. Nord J Psychiatry 2014;68:507–12.
2. SBU. Diagnostik och uppföljning av förstämningssyndrom. En systematisk litteraturöversikt. Stockholm: Statens beredning för medicinsk utvärdering (SBU); 2012. SBU-rapport nr 212. ISBN 978-91-85413-52-2. Available from: http://www.sbu.se/forstamningssyndrom 2012.
3. Kujanpaa T, Ylisaukko-Oja T, Jokelainen J, Linna M, Timonen M. Comparative cost analysis of generalized anxiety disorder and major depressive disorder patients in secondary care from a national hospital registry in Finland. Nord J Psychiatry 2014;68:306–10.

4. Rush AJ, Warden D, Wisniewski SR, Fava M, Trivedi MH, Gaynes BN, et al. STAR*D: revising conventional wisdom. CNS Drugs 2009;23: 627–47.
5. Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control Clin Trials 2004;25:119–42.
6. Nordanskog P, Hulten M, Landen M, Lundberg J, von Knorring L, Nordenskjold A. Electroconvulsive therapy in Sweden 2013: Data from the national quality register for ECT. J ECT 2015;31:263–7.
7. Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the consortium for research in electroconvulsive therapy (CORE). Arch Gen Psychiatry 2006;63:1337–44.
8. Kellner CH, Knapp R, Husain MM, Rasmussen K, Sampson S, Cullum M, et al. Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. Br J Psychiatry 2010;196:226–34.
9. Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA. Effectiveness of electroconvulsive therapy in community settings. Biol Psychiatry 2004;55:301–12.
10. Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, et al. Resistance to antidepressant medications and short-term clinical response to ECT. Am J Psychiatry 1996;153:985–92.
11. Heikman P, Katila H, Sarna S, Wahlbeck K, Kuoppasalmi K. Differential response to right unilateral ECT in depressed patients: impact of comorbidity and severity of illness [ISRCTN39974945]. BMC Psychiatry 2002;2:2.
12. Rasmussen KG. Do patients with personality disorders respond differentially to electroconvulsive therapy? A review of the literature and consideration of conceptual issues. J ECT 2015;31:6–12.
13. Nordenskjold A, von Knorring L, Brus O, Engstrom I. Predictors of regained occupational functioning after electroconvulsive therapy (ECT) in patients with major depressive disorder – a population based cohort study. Nord J Psychiatry 2013;67:326–33.
14. Deng ZD, Lisanby SH, Peterchev AV. Coil design considerations for deep transcranial magnetic stimulation. Clin Neurophysiol 2014;125:1202–12.
15. SBU. Transkraniell magnetstimulering vid depression. En systematisk litteraturöversikt. Stockholm: statens beredning för medicinsk utvärdering (SBU); 2009. SBU-rapport nr 192. ISBN 978-91-85413-29-4. Available from: http://www.sbu.se/sv/Publicerat/Gul/Transkraniell-magnetstimulering-vid-depression/. 2009.
16. Berlim MT, van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med 2014;44:225–39.
17. Berlim MT, Van den Eynde F, Jeff Daskalakis Z. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. Neuropsychopharmacology 2013;38:543–51.
18. Ren J, Li H, Palaniyappan L, Liu H, Wang J, Li C, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry 2014;51:181–9.
19. Levkovitz Y, Harel EV, Roth Y, Braw Y, Most D, Katz LN, et al. Deep transcranial magnetic stimulation over the prefrontal cortex: evaluation of antidepressant and cognitive effects in depressive patients. Brain Stimul 2009;2:188–200.
20. Kedzior KK, Gellersen HM, Brachetti AK, Berlim MT. Deep transcranial magnetic stimulation (DTMS) in the treatment of major depression: an exploratory systematic review and meta-analysis. J Affect Disord 2015;187:73–83.
21. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
22. Levkovitz Y, Isserles M, Padberg F, Lisanby SH, Bystritsky A, Xia G, et al. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatry 2015;14:64–73.
23. McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, et al. The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis. Health Technol Assess 2007;11:1–54.
24. Haynes RB, McKibbon KA, Wilczynski NL, Walter SD, Werre SR, Hedges Team. Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. BMJ 2005;330:1179.