KEY MESSAGES OF THE ORIGINAL PUBLICATION

- Repetitive transcranial magnetic stimulation (rTMS) is generally safe and well-tolerated.
- Compared with sham intervention, rTMS has a small short-term effect for improving depression (< 6 months; very low to low quality of evidence). This effect cannot be assessed in the long-term (follow-up data limited to 1-6 months).
- Insufficient evidence hampers to prove if rTMS is as effective and safe as electroconvulsive therapy (ECT).

SUMMARY OF THE ORIGINAL PUBLICATION

Context

Treatment-resistant major depressive disorder (TRD) usually refers to major depressive disorder (MDD) that does not respond satisfactorily to at least two adequate trials of antidepressant monotherapy lasting 6-12 weeks each.

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation technique based on the principle of electromagnetic induction of an electric field in the brain, delivered as a series of pulses.

Method

The systematic literature review (up to January 2017) and meta-analyses aimed at summarising the effectiveness and safety of rTMS in adult patients with TRD, compared either with sham stimulation (delivered with a sham coil), or with electro-convulsive therapy (ECT, involving 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).
Results

The EUnetHTA authors selected the Health Quality Ontario (HQO) systematic review and updated it with two more recent randomized controlled trials (RCTs; Solvason et al. 2014 and Kang et al. 2016). Altogether, 25 primary studies compared rTMS (n=615) with sham stimulation (n=565), and 6 primary studies compared it with electroconvulsive therapy (ECT) (n=133 in each arm).

In comparison with sham, TRD patients treated with rTMS may be twice more likely to experience treatment response (defined as a ≥50 percent improvement from baseline on a depression rating scale) and remission (defined as a depression rating scale score ≤ to a specific cut-off that defines the normal range, e.g. score ≤ 7 on the Hamilton Depression Rating Scale).

On average, rTMS significantly reduced depression scores by about 2.31 points more than sham, but this reduction was not considered clinically relevant (threshold of 3.5 points defined a priori as clinically important). No statistically significant differences were obtained between ECT and rTMS regarding response and remission rates. On average, ECT decreased depression scores by about 5.97 points more than rTMS (both statistically and clinically significant), thereby favouring ECT.

Safety

The most common side-effect presented in the rTMS versus sham studies was headache with rates ranging from 0% to 60% in the rTMS group and 0% to 50% in the sham group. 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. No serious safety concerns were identified in the rTMS versus ECT comparison.

Clinical effectiveness

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Remission rate</th>
<th>Weighted mean difference in depression scores</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response rate</strong></td>
<td><strong>Remission rate</strong></td>
<td><strong>rTMS vs sham</strong></td>
</tr>
<tr>
<td><strong>Comparison with Sham</strong></td>
<td><strong>rTMS vs sham</strong></td>
<td><strong>rTMS vs sham</strong></td>
</tr>
<tr>
<td>Results</td>
<td>RR = 1.82</td>
<td>RR = 2.16</td>
</tr>
<tr>
<td></td>
<td>95% BI: 1.18 to 2.82</td>
<td>95% BI: 1.42 to 3.29</td>
</tr>
<tr>
<td></td>
<td>p = 0.0068</td>
<td>p = 0.0003</td>
</tr>
<tr>
<td>Quality of evidence *</td>
<td>Very low</td>
<td>Low</td>
</tr>
<tr>
<td>Comparison with ECT</td>
<td><strong>rTMS vs ECT</strong></td>
<td><strong>rTMS vs ECT</strong></td>
</tr>
<tr>
<td>Results</td>
<td>RR = 1.72</td>
<td>RR = 1.44</td>
</tr>
<tr>
<td></td>
<td>95% BI: 0.95 to 3.11</td>
<td>95% BI: 0.64 to 3.23</td>
</tr>
<tr>
<td></td>
<td>p = 0.072</td>
<td>p = 0.375</td>
</tr>
<tr>
<td>Quality of evidence *</td>
<td>Very low</td>
<td>Very low</td>
</tr>
</tbody>
</table>

AE: absolute effect, CI: confidence interval, ECT: electroconvulsive therapy, MD: mean difference, p: p-value, RD: risk difference, RR: risk ratio, rTMS: repetitive transcranial magnetic stimulation

Quality of the publication

The Health Quality Ontario systematic review was independently appraised by two authors of the EUnetHTA report and was scored 9/11 on the AMSTAR tool, demonstrating good methodological quality. Assessment of the RCTs’ risk of bias and strength of evidence was based on the Cochrane risk of bias approach and on GRADE.

Belgian context

In a study conducted in 2008 by 172 Belgian sentinel general practices, 1 year incidence rates for GP-diagnosed depression were estimated to be 719/100 000 for men and 1440/100 000 for women. Of these patients, 31% were GP-diagnosed with a mild depression, 50% with a moderate depression and 19% with a severe depression. This is certainly an underestimate as not all patients with a depression go to a GP (Boffin et al. 2012). Results of the 2013 health interview survey from the Scientific Institute of Public Health (WIV-ISP) indicated a self-reported prevalence of depression of 15% (2013). A 2011 survey from the European Commission (Consortium EPREMED) reports a lifetime prevalence for major depression of 12.4% in the general population. Mental diseases, in particular depression, are the first cause of disability in Belgium.

Mental health care is high on the political agenda of the current Belgian Minister of Social Affairs and Public Health with, among others, the recent publication (02/2017) of updated recommendations for the general practitioners to help them in the identification, diagnosis, treatment and follow-up of depression in adults. These recommendations also include the referral of treatment-resistant depressive patients towards psychiatrists who will prescribe adapted treatments.

Several rTMS devices received CE marking and are available in Belgium. The technique is however not reimbursed in Belgium.
REFERENCES


What is the EUnetHTA Joint Action?

The overall objective of the EUnetHTA Joint Action is to foster collaboration and knowledge sharing between European public HTA agencies, with the aim of increasing the efficiency and quality of technology assessments and promoting their uptake in the national health policy decision-making processes. The present collaborative assessment is part of the EUenetHTA Joint Action 3 WP 4 whose aim is to produce a structured information for rapid or full/comprehensive HTAs in which 2 or more countries and/or organisations work together to prepare shared products or agreed outcomes (more info: www.eunethta.eu)

What is GRADE?

GRADE (Grading of Recommendations Assessment, Development and Evaluation) offers a system for rating quality of evidence in, amongst other, systematic review. More information on GRADE can be found in the GRADE website and in the KCE process book.

What is the Cochrane’s tool for assessing risk of bias?

This Cochrane’s tool for assessing risk of bias provides judgements made on six domains including randomisation sequence generation, allocation concealment methods, blinding (participants, personnel and outcome assessors), incomplete outcome data, selective outcome reporting, and any other relevant biases. For each domains, one of the following risk level can be attributed: low, unclear, or high risk.