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

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Executive summary

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**Background**

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that can be used to target neuronal circuitry implicated in neuropsychiatric disorders, such as the dorsolateral prefrontal cortex (DLPFC) in depression. rTMS has been reported to be as effective as electroconvulsive therapy (ECT), which is currently the most powerful treatment available for severe depression.

**Objective**

The aim of this study was to investigate if rTMS was as effective as ECT in treating major depressive episodes and to perform a cost-effectiveness analysis.

**Methods**

**Design**

The study was a single-blind pragmatic multicentre randomised controlled trial (RCT) with 6 months of follow-up to test equivalence of rTMS with ECT.

**Setting**

The study took place in the South London and Maudsley NHS Trust and Pembury Hospital in the Invicta Mental Health Trust in Kent.

**Participants**

Right-handed adult patients referred for ECT for treatment of a major depressive episode (DSM-IV) were assessed. During the 2.5-year trial period, 260 patients were referred for ECT, of whom 46 entered the trial. The main reason for not entering the trial was not consenting to ECT while being formally treated under the UK Mental Health Act 1983.

**Interventions**

Patients were randomised to receive a 15-day course of rTMS of the left DLPFC ($n = 24$; 20 trains per day, 5 seconds of treatment at 10 Hz, 110% of motor threshold) or a course of ECT ($n = 22$; stimulus dosing method, 1.5 times the seizure threshold, course length decided by referring physician).

**Main outcome measures**

Patients were assessed before randomisation, at end of treatment and at the 6-month follow-up. Primary outcome measures were the 17-item Hamilton Rating Scale for Depression (HRSD) and proportion of remitters (defined as HRSD score $\leq 8$) at the end-of-treatment time point. Secondary outcomes included self-ratings for mood on the Beck Depression Inventory-II (BDI-II) and visual analogue mood scales (VAMS), the Brief Psychiatric Rating Scale (BPRS), plus subjective and objective side-effects. Low scores on the BDI-II, VAMS and BPRS are positive in terms of health. The results were analysed on an intention-to-treat basis. Cost data were collected using the Client Service Receipt Inventory and the Short Form with 36 Items (SF-36) was used to obtain quality of life measures. Health economic outcomes were cost of treatments, costs incurred during the 6-month follow-up period and gains in quality-adjusted life-years (QALYs).

**Data analysis**

HRSD and other clinical outcome scores were compared between groups using an analysis of covariance (ANCOVA) model with baseline scores as covariates. Trial data that became available before recruitment began allowed revision of samples sizes such that 22 subjects per treatment group would be sufficient to have 80% power to demonstrate, using a one-sided equivalence test at the $\alpha = 0.5$ level, that the mean reduction in HDRS score using rTMS would be no more than 25% less than that achieved using ECT.

**Results**

One patient was lost to follow-up at end of treatment and another eight at 6 months. The end-of-treatment HRSD scores were lower for ECT (95% confidence interval (CI) 3.40 to 14.05, $p = 0.002$), with 13 (59%) achieving remission compared with four (17%) in the rTMS group ($p = 0.005$). However, HRSD scores did not differ
between groups at 6 months. BDI-II, VAMS and BPRS scores were lower for ECT at end of treatment and remained lower after 6 months. Improvement in subjective reports of side-effects following ECT correlated with antidepressant response. There was no difference between the two groups before or after treatment on global measures of cognition.

Although individual treatment session costs were lower for rTMS than ECT, the cost for a course of rTMS was not significantly different from that for a course of ECT as more rTMS sessions were given per course. Service costs were not different between the groups in the subsequent 6 months but informal care costs were significantly higher for the rTMS group (p = 0.04) and contributed substantially to the total cost for this group during the 6-month follow-up period. There was also no difference in gain in QALYs for ECT and rTMS patients. Analysis of cost-effectiveness acceptability curves demonstrated that rTMS has very low probability of being more cost-effective than ECT.

**Limitations**

Rater blinding was not maintained and is a potential source of bias. However, similar results were obtained on both observer- and self-rated measures. The optimal parameters for administering rTMS to achieve an antidepressant effect are not yet known.

**Conclusions**

ECT is a more effective and potentially cost-effective antidepressant treatment than 3 weeks of rTMS as administered in this study. Optimal treatment parameters for rTMS need to be established for treating depression. More research is required to refine further the administration of ECT in order to reduce associated cognitive side-effects while maintaining its effectiveness.

**Recommendations for further research**

There is a need for large-scale, adequately powered RCTs comparing different forms of ECT. The next generation of randomised trials of rTMS should also seek to compare treatment variables such as stimulus intensity, number of stimuli administered and duration of treatment, with a view to quantifying an effect size for antidepressant action.

**Publication**

The Health Technology Assessment (HTA) programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

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Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read monograph series *Health Technology Assessment*.

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Reports are published in the HTA monograph series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 98/11/04. The contractual start date was in August 2001. The draft report began editorial review in September 2005 and was accepted for publication in February 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

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