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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.

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Abstract

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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Objective: To investigate if repetitive transcranial magnetic stimulation (rTMS) was as effective as electroconvulsive therapy (ECT) in treating major depressive episodes and to perform a cost-effectiveness analysis.
Design: A single-blind pragmatic multicentre randomised controlled trial (RCT) with 6 months of follow-up to test equivalence of rTMS with ECT.
Setting: 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 dorsolateral prefrontal cortex ($n = 24$) or a course of ECT ($n = 22$).
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 $\leqslant 8$) 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 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).
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, with 13 (59%) achieving remission compared with four (17%) in the rTMS group. 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 and contributed substantially to the total cost for this group during the 6-month follow-up period. There also was 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.

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. 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.

Contents

List of abbreviations

AMI	Autobiographical Memory Interview
ANCOVA	analysis of covariance
APB	abductor pollicis brevis
BDI	Beck Depression Inventory
BPRS	Brief Psychiatric Rating Scale
CAMCOG	Cambridge Cognitive Examination
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CSRI	Client Service Receipt Inventory
CSSES	Columbia ECT Subjective Side Effects Schedule
df	degrees of freedom
DLPFC	dorsolateral prefrontal cortex
ECT	electroconvulsive therapy
EEG	electroencephalogram
HRQoL	health-related quality of life
HRSD	Hamilton Rating Scale for Depression
ICER	incremental cost-effectiveness ratio
MDD	major depressive disorder
MMSE	Mini Mental State Examination
MT	motor threshold
NICE	National Institute for Health and Clinical Excellence
QALY	quality-adjusted life-year
rTMS	repetitive transcranial magnetic stimulation
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	standard deviation
SF-36	Short Form with 36 Items
ST	seizure threshold
VAMS	visual analogue mood scales

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

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 $\leqslant$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 α = 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.

Chapter 1

Objective of the study

The objective of this study was to carry out a pragmatic randomised controlled trial of repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT) for treating major depressive episodes in patients referred for ECT, including a cost-effectiveness analysis. A pragmatic design was chosen so that the trial would resemble and reflect routine practice as much as possible such that the results would be generalisable throughout the NHS.

Chapter 2
Introduction

Depression and ECT

Major depressive disorder (MDD)[1] is one of the leading causes of the global burden of disease,[2] with 13% of men and 21% of women affected at some point in their lives. Treating depression in England and Wales costs £420 million per year and indirect costs exceed £3 billion.[3] These figures can only be rough estimates but are probably of the correct order of magnitude. Major depression has a high relapse rate and recurring episodes are associated with increasing risk of chronicity coupled with long-term psychosocial impairment and distress, loss of productivity, disruption of normal social relationships and suicide.[4]

It is important, therefore, that all severe episodes be treated early and vigorously to reduce disability and prevent morbidity.[5] However, up to 30% of patients with severe depression fail to respond sufficiently to trials of antidepressant medications given at adequate doses for at least 6 weeks.[6,7] Frequently these patients (and also severely ill patients and those unable to tolerate antidepressant medication) are treated with ECT. Even though 'medication resistance' is associated with a poorer response to ECT, at least 50% of the 'resistant' group will respond; in fact, response rates to ECT may be even higher, up to 85%, in patients who have not failed a medication trial.[8]

Acceptability of ECT

A recent meta-analysis has confirmed that ECT is one of the most effective treatments available for severe depression[9] and this indication has been approved in the UK by the National Institute for Health and Clinical Excellence (NICE).[10] However, it is rarely a first- or even second-line treatment and is generally reserved for either very ill patients or patients refractory to standard treatments. The reasons for this are not clear but are most likely to be due to issues of acceptability of ECT related to repeated general anaesthesia, application of an electric charge through the brain, induction of a seizure and cognitive side-effects. Interestingly, patients treated with ECT have been reported to develop a more positive attitude towards it, as do their relatives.[11–14] Nonetheless, there still remains the important issue of adverse cognitive side-effects of ECT.

Cognitive dysfunction, depression and ECT

In severe depression, there is a consistent picture of impaired memory function and frontal-executive deficits.[15,16] Such changes are consistent with the predominantly prefrontal patterns of cerebral blood-flow abnormalities observed in neuroimaging studies.[17,18] Depression-related cognitive impairment typically improves on remission of the mood disturbance, a change associated with normalisation of frontal metabolic function.[18] Cognitive changes due to depression can be distinguished from those due to ECT. The immediate adverse cognitive side-effects of ECT result mainly from the anaesthesia and seizure. Headache, disorientation and memory complaints are the most common subjective side-effects.[19] Both subjective complaints[19] and objective measures of cognitive impairment[20] can worsen during treatment, despite improvements in subjective mood. Significant improvements in cognitive function after 6 months[21] and even 4 years[22] following ECT have been reported.

However, more recently there has been growing concern that ECT may cause longer lasting cognitive impairment that is not related to enduring depression.[23] In particular, ECT has been reported to cause retrograde amnesia and this is more problematic with bilateral than unilateral ECT, even high-dose unilateral ECT.[24,25] There is clearly a need to develop ECT further to reduce its side-effects while simultaneously maintaining its efficacy. Alternatively, another treatment as effective as ECT but without its side-effects or problems with acceptability would be welcomed by both patients and physicians.

Repetitive transcranial magnetic stimulation: how it works

One potential alternative to ECT might be rTMS.[26,27] TMS works by passing an electric

current through a hand-held coil and using this to focus an electromagnetic field, that is changing over time, on to the scalp.[28] The magnetic field rapidly falls off 1–2 cm from the surface of the cortex. Following Faraday's law, this induces eddy currents (proportional to the rate of change of the magnetic field) in the underlying cerebral cortex, thereby stimulating neural tissue, probably by depolarisation. In ECT, high voltages are required to enable an electrical stimulus to pass through the strongly insulating scalp and skull, whereas pulsed magnetic fields readily pass through unattenuated to produce electrical effects in the cortex. Hence TMS, as opposed to ECT, can induce cortical electrical activity without causing a seizure, that is, it is sub-convulsive, and does not require any anaesthesia.

TMS technology was initially developed to map cortical function and investigate the integrity of corticospinal pathways by stimulating the motor cortex and observing peripheral muscle activity and motor evoked potentials.[29,30] Contemporary machines can produce large, rapidly changing magnetic forces and are capable of precisely delivering repetitive pulses of up to 50 stimuli per second to targeted cortical regions. Depending on the settings used, small induced currents can then make brain areas below the coil more or less active. For example, rapid (i.e. 1–20 Hz) rTMS is activating whereas slow (i.e. <1 Hz) rTMS is inhibitory.[31] Single-pulse TMS and rTMS have been demonstrated to affect many brain functions temporarily, including movement, visual perception, memory, reaction time, speech and mood, and have been widely used to investigate brain function.[26,27,32,33]

Transcranial magnetic stimulation: safety issues

TMS is considered to be a safe tool for neurological investigation and in limited studies has not been reported to cause any changes to cerebral structures on either histological examination or neuroimaging.[34,35] Nor is there any evidence of immediate cognitive side-effects such as occur with ECT,[36–38] although few data are available on possible long-term cognitive sequelae. There is a risk of inducing seizures with rTMS due to repetitive cortical activation (see Chapter 3 for a detailed discussion of the administration and safety of rTMS). Most of this increased risk has been attributed to giving stimuli too frequently, at too high an intensity, and without sufficient time gaps between trains of stimuli.[39] Clinical and research experience with rTMS has informed safety guidelines for treatment parameters.[40–42]

rTMS and depression

Early trials of rTMS, mostly uncontrolled and open with small numbers, indicated that it might be beneficial in up to 50% of patients with treatment resistant depression.[43–46] The studies also helped to refine some of the safety aspects and the parameters required for therapeutic application of rTMS. These include the efficacy and safety of sub- and moderately supra-motor threshold (MT) stimulus intensities (90–110%), the optimal frequency of fast stimuli (10–20 Hz), the duration of treatment sessions and number of sessions required (at least five), and also the identification of the left dorsolateral prefrontal cortex (DLPFC) as possibly the best treatment site. A theoretical mechanism for this lateralised effect on mood may relate to the evidence cited above that focal reductions in glucose metabolism and blood flow in the left DLPFC are associated with major depression and that these abnormalities normalise with treatment and recovery.

The first double-blind, randomised, placebo-controlled study with a multiple cross-over design was carried out by Pascual-Leone and colleagues (1996)[47] on 17 patients with medication-resistant psychotic depression. Their aim was to study the effect of sub-threshold (90%) stimulation at 10 Hz of the left DLPFC. Each patient received five treatment courses in randomised order for 5 days at the beginning of each month over 5 months: real and sham left DLPFC, real and sham right DLPFC and real vertex stimulation. Each session comprised 2000 stimuli daily (20 trains of 10-s duration separated by 60-s intervals). Only left DLPFC rTMS resulted in a statistically significant decrease in Hamilton Rating Scale for Depression (HRSD) scores (from a mean of 25.2 to 13.8) and after 5 days 11 of 17 patients showed improvement, which then diminished over the next 2 weeks. This study is unusual in the high degree of cooperation and compliance that the researchers obtained from such severely ill patients.

Nevertheless, many subsequent studies found similar results. For example, George and colleagues[48] examined the effect of daily left DLPFC rTMS (80% of MT, 20 Hz, 20 trains of 2 s each, 60 s apart, i.e 800 pulses per session) on 12 patients with major depressive episodes. They used a placebo-controlled, cross-over design and found statistically significant reductions in HDRS

scores (mean reduction 5.25) after two weeks (ten sessions) of rTMS treatment. In another open trial, Figiel and colleagues[49] treated 50 patients with treatment refractory depression with rTMS to the left DLPFC for five consecutive weekdays (110% of MT, 10 Hz, 10 trains of 5 s each, 30 s apart). There were 21 (42%) responders who had a 60% reduction in their pretreatment HRSD scores. Interestingly, 57% (16/28) of patients aged under 65 years responded whereas only 23% (5/22) of patients aged over 65 years responded.

Not all early trials of rTMS in depression were positive. Loo and colleagues[50] studied 18 treatment-resistant patients with DSM-IV major depression who were randomly allocated to 2 weeks (10 consecutive weekdays) of real or sham rTMS (110% of MT, 10 Hz, 30 trains of 5 s each, 30 s apart) while continuing to take antidepressant medication. During the 2-week study period, both groups improved equally well with a reduction in HRSD scores similar to that reported in George and colleagues' study.[48] The researchers expressed some surprise at their finding, considering the refractory nature of the depression being treated, but could not identify any factors for this beyond increased clinical contact and the possibility of the repetitive sham treatments actually delivering a therapeutic stimulus.

Other studies have investigated using slow rTMS to **inhibit** the **right** DLPFC to rectify any possible imbalance in prefrontal activities in depression. A controlled double-blind study of rTMS in 70 patients with DSM-IV major depression reported that nearly 50% of the real rTMS group, compared with 25% of the sham group, decreased their HDRS scores by more than 50% from pretreatment levels.[51] rTMS was delivered over 2 weeks to the **right** DLPFC at **low** frequency (1 Hz) and 110% of MT. Two trains of 60 stimuli were delivered for 1 minute each with a 3-minute interval. This was the first substantial trial of using low-frequency right-sided rTMS and revealed that the definitive treatment parameters for rTMS in depression remained to be finalised (and they still do), and that there is probably a range of potentially effective parameter sets. Furthermore, it is not yet clear what patient characteristics will best predict a response to rTMS or what the long-term consequences of rTMS are with regard to maintenance of antidepressant effect, relapse rate and side-effects.

Several meta-analyses of controlled trials (ranging from five to 14 trials) of rTMS in depression have been published since the present study began.[52–57] In general, these have highlighted the large degree of heterogeneity that exists between studies and the variable, often low, standard of published trials. Indeed, because of this, one group of researchers felt that a formal meta-analysis was not possible.[58] For example, both crossover and parallel group studies are often included together, whereas it is usually obvious to the trial subject that there is a difference between the experience of real and sham rTMS and thus blinding is lost. The meta-analyses are further compromised by the use of different types of 'sham' rTMS. For example, many studies have delivered sham rTMS by angling the coil away from the scalp rather than using purpose-built sham coils. However, it appears that this type of 'sham' treatment can actually have a 'real' effect as the magnetic field can still penetrate through to the underlying cortex.[59,60] While the earlier meta-analyses[52,53] are cautiously supportive of a therapeutic role for rTMS in depression and discuss the need for more and better trials, the more recent meta-analyses[56,57] are less supportive.

What is clear from the meta-analyses, however, is that in order to develop rTMS as a treatment for depression, further research is required to optimise treatment parameters (e.g. stimulus site, intensity and frequency of stimuli, duration of treatment).

Comparisons between ECT and rTMS for treating depression

During the course of the present study, several randomised trials comparing up to 4 weeks of rTMS with ECT for treating depression have been published. Initial randomised studies suggested that effectiveness may approach that of ECT, particularly in non-delusional depression.[61–64] Relapse rates over 6 months in responders to rTMS or ECT in randomised studies have been reported to be similar at about 20% for both treatments.[65]

Quality of life and costs of ECT and rTMS

To facilitate formulating policies about the use of resources, it is important to translate the burden of illness and cost of treatment into economic values. Therefore, when a new treatment for affective disorders becomes available that is a potential alternative to an established treatment, as rTMS is for ECT, it is essential not only to

demonstrate the new treatment's effectiveness but also to establish its cost and compare this with the established treatment in a cost-effectiveness analysis.

ECT has been reported to be associated with improved quality of life that is evident within the first month post-treatment and that can be maintained for up to 1 year.[66,67] Quality of life data following treatment with rTMS are not available. There are no cost-effectiveness data currently available for ECT and a recent attempt to generate a model proved inconclusive, mainly due to a lack of suitable randomised controlled trial data and uncertainty around the optimal treatment parameters for ECT.[68] No reports have yet been published on the costs associated with using rTMS to treat depression. However, using the USA insured population and based on the assumption that rTMS is equally effective as ECT, a decision analysis model of cost-effectiveness concluded that rTMS would cost less that ECT.[69]

Chapter 3
Methods

Design

The study was a two-group parallel design pragmatic randomised controlled trial[70] of rTMS versus ECT for patients with a major depressive episode (DSM-IV[1]) who had been referred for ECT. Following baseline assessment, consenting patients were randomly allocated to a course of either ECT or rTMS by an independent third party who was a member of the academic staff but otherwise had no involvement with the trial or relevant researchers. A protected and concealed computer database (Microsoft Access) containing the randomisation list was used to ensure allocation concealment. Randomisation was stratified by health trust. Subsequent ratings were performed by trained research workers blind to treatment modality.

Because of the obviously different natures of the two treatments, it was not possible for patients to be blind to their allocated treatment. Patients and their healthcare staff were asked not to discuss treatment details with the raters. To test blinding, raters were asked to guess what treatment had been allocated after the end-of-treatment assessment. Apart from the interventions under study, both groups continued to receive the standard treatment package usually prescribed by the referring NHS physician and care team.

Trial participants

Patients were recruited from six hospitals in the South London and Maudsley (SLaM) NHS Trust and Pembury Hospital in the Invicta Mental Health Trust in Kent. ECT was administered at three of the South London and Maudsley facilities (The Maudsley Hospital, Bethlem Royal Hospital and Lewisham General Hospital) two of which also provided rTMS (The Maudsley and Bethlem Royal Hospitals). Both ECT and rTMS were administered at Pembury Hospital. Recruitment was between January 2002 and August 2004. Right-handed patients aged over 18 years referred for ECT to treat a major depressive episode were invited to enter the study. Diagnosis was confirmed using the mood disorders module of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID).[71]

Exclusion criteria were inability to provide informed consent; unable to have rTMS due to presence of metallic implants or foreign bodies or previous history of seizures; history of substance misuse in the past 6 months; any medical condition rendering the patient unfit to have a general anaesthetic; ECT or rTMS in the previous 6 months; evidence of dementia or other Axis 1 diagnosis. The study was approved by the local ethics committees and all participants provided written informed consent.

Interventions

rTMS was given by research physicians using the Magstim Super Rapid stimulator (Magstim Co. Ltd, Whitland, UK) with a figure-of-eight coil kept cooled on ice, essentially as previously described.[61,63] Research physicians kept social interactions with patients to a minimum. In the first session, the MT of the abductor pollicis brevis (APB) site in the left motor cortex was determined by visual inspection using a method of limits.[72] The MT is the minimum stimulus required to activate the APB and was used to calibrate the treatment stimulus. Patients were seated in a reclined chair and wore cotton skull caps upon which target points were marked. Using single stimuli at the same intensity (e.g. 40% of output), the stimulating coil was moved over the left motor cortex in a straight line in 1-cm steps to map the activation point of the APB. At the same time, the subjects were actively contracting their hand muscles in order to lower the threshold for stimulation, thus making the stimulus more focal and also making it easier to identify twitching of the APB. Having identified the best spot for activation of the APB, subjects then relaxed and the resting MT was determined. Continuing to stimulate at the APB point, the stimulus intensity was lowered to well below threshold and then increased 2% at a time, with six stimuli at each level of intensity until twitching was apparent in three or more of the six stimuli in each group. This stimulus strength was the MT for the APB point. The point for stimulation of the DLPFC was 5 cm anterior to the APB point.

Stimulations were given at 110% of the MT to the left DLPFC deemed to be located 5 cm anterior to

the APB point in the parasagittal plane. Each treatment session entailed 20 trains of rTMS at 10 Hz for 5 seconds with 55-second inter-train intervals. A full course of rTMS comprised 15 daily sessions (total of 15,000 magnetic pulses) administered on weekdays beginning on a Monday.

ECT was administered twice weekly with hand-held electrodes and according to Royal College of Psychiatrists' guidelines.[73] Methohexitone (0.75–1.0 mg/kg) was used for anaesthetic induction and suxamethonium (0.5–1.0 mg/kg) as muscle relaxant. The Thymatron DGx device (Somatics Inc., Lake Bluff, IL, USA) was used at the three SLaM sites and the Mecta SR2 device (Mecta Corp., Lake Oswego, OR, USA) was used at the Pembury Hospital site. Both devices deliver constant-current, bi-directional brief pulses. Seizure durations were measured by dual-channel EEG monitoring. Patients' seizure thresholds (STs) were established by a method of limits at the first treatment session as previously described.[74] Subsequent treatments were given at 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT. The stimulus charge was titred upwards as required during the treatment course using standard stimulus dosing protocols.[73] The number of ECT treatments depended on the patient's response as determined by the referring physician.

Outcomes

The primary outcome measure for this study was the 17-item HRSD[75] score at the end of the allocated treatment and rate of remission (defined as HRSD ⩽8). Secondary outcomes included subjective ratings of depression with both the Beck Depression Inventory-II (BDI-II)[76] and aggregated visual analogue mood scales (VAMS) score,[77] global measure of psychopathology on the Brief Psychiatric Rating Scale (BPRS)[78] and relapse rate after 6 months (defined as HRSD ⩾12). The VAMS consists of seven brief visual scales for subjective ratings (sad, confused, afraid, happy, tired, angry and energetic), which descend vertically 100 mm from a 'neutral' option. The VAMS has been demonstrated to be both reliable and valid in healthy young adult and elderly controls and also to be a sensitive marker of treatment response to ECT.[77] The higher the score on all of these measures the greater is the severity of depression and related symptoms. Economic outcomes included costs and quality-adjusted life-years (QALYS) gained (see below).

Baseline data obtained by interview and review of hospital records also included age, sex, duration of current major depressive episode, previous history of depression and ECT, presence of psychotic symptoms (i.e. delusions and/or hallucinations) as detected on the SCID assessment, level of treatment resistance as measured by the number of adequate previous courses of antidepressants and augmentation strategies, and current psychotropic medications. End-of-treatment assessments were carried out 2–3 days after the final treatment in the allocated course and patients were also followed up for 6 months.

Subjective symptoms potentially attributable to either ECT or rTMS were assessed with a shortened version of the Columbia ECT Subjective Side Effects Schedule (CSSES)[19,79] that was modified to document potential rTMS side-effects (e.g. seizure induction, scalp discomfort, hearing loss) and any other unpredictable adverse events due to either rTMS or ECT. The symptoms assessed by the CSSES can be grouped into four main categories: somatic, cognitive, mood and psychomotor agitation. The cognitive symptoms embedded within the CSSES allowed us to generate a self-rated measure for cognition by totalling the number of positive responses to the following five questions: Have you had trouble recalling people's names? Have you felt confused or disorientated? Have you had any memory problems? Have you had trouble concentrating? Have you had trouble holding in your memory new things you have learned?

Changes in cognitive function, due either to treatment side-effects or to treatment response, were recorded. Baseline global cognitive function was assessed using the Cambridge Cognitive Examination (CAMCOG) section of the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) interview schedule,[80] from which it is also possible to generate a score for the Mini Mental State Examination (MMSE).[81] It provides a total score (maximum 107) plus subscale scores for different aspects of cognition and has been used previously to study cognition in depression.[82] Lower scores reflect poorer performance on testing.

In addition, the following battery of tests focusing on memory and frontal-executive function were also administered:

1. Measures of immediate short-term memory plus attention and working memory were obtained using the Forward and Backward Digit Spans.[83]

2. Retrograde autobiographical memory was assessed using Sections 2 and 3 of the Autobiographical Memory Interview (AMI) to cover recent (i.e. within the past 5 years) and more remote (i.e. early adulthood) personal memories.[84]
3. Motor and psychomotor speed were rated with the Trail Making Test (Part A);[85] the Symbol Digit Modalities Test,[86] a sensitive measure of psychomotor speed adapted from the Digit Symbol Subtest of the Wechsler Adult Intelligence Test;[83] and the Grooved Pegboard Test (Lafayette Instrument Co., Lafeyette, IN, USA),[87] a test of speeded fine eye–hand coordination.
4. Frontal/executive function was further rated by the Trail Making Test (Part B).[85]

Sample size and statistical methods

This trial was first proposed in 1999 following a call by the NHS Health Technology Assessment (HTA) programme for such a study. At that time no comparison data were available on rTMS and ECT for depression. Using response data from a large series of severely depressed patients treated with ECT in which the mean percentage decline in HRSD depression rating scores was 72.5 (23.7)%,[88] we initially estimated that 76 subjects would be required in each treatment group to have 80% power to demonstrate, using a one-sided equivalence test at the $\alpha = 0.5$ level, that the mean reduction in HRSD score using rTMS was no more than 13% (corresponding to 3.0 points on the 24-item HRSD[88]) less than that achieved using ECT.

Shortly before this trial began, and in the early stages of recruitment, several reports were published indicating that rTMS was not better than ECT for depression but that its effectiveness might approach that of ECT.[61–64] At the same time, recruitment to this trial was slower than expected despite multiple centres, possibly due to an ongoing reduction in referrals for ECT at both national and local levels.[89,90] As a result, the initial sample size estimations were reviewed. It was deemed that if rTMS had at least 75% of the effectiveness of ECT in reducing depression scores, then rTMS would merit clinical interest for this difficult-to-treat population, particularly in the light of its safety and good side-effect profile. This change to the study methodology was approved by both the trial's steering committee and data monitoring and ethics committee; the NHS HTA was informed of the changes. Using the same ECT response data,[88] it was estimated 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 HRSD score using rTMS would be no more than 25% less than that achieved using ECT.

All outcomes were analysed on an intention-to-treat basis. HRSD scores were compared between the ECT and rTMS treatment arms using an analysis of covariance (ANCOVA) model. The model used HRSD scores at end of treatment and follow-up time points as dependent variables and included main effects of time (end of treatment or follow-up) and treatment plus their interaction. In addition, prerandomisation baseline HRSD scores were included as a covariate, as were NHS Trusts to adjust for centre effects. End of treatment was defined as the last treatment received within an allocated course, irrespective of the total number of treatments. Whereas rTMS courses were predetermined to have fixed durations, i.e. 15 weekdays, the ECT courses were of variable duration. Therefore, within-treatment-course ratings were not included in analyses. Standard errors that were robust against correlations within subject clusters were used to account for the two repeated measures per subject. If the treatment × time interaction tested significant at the 5% significance level, two *post hoc* comparisons were carried out to compare the treatment arms separately at the end-of-treatment and follow-up time points (at the Bonferroni adjusted significance level of $5/2 = 2.5\%$). If the interaction term was not statistically significant, it was excluded from the model and the main effect of treatment evaluated to estimate the treatment effect. Standardised effect sizes were calculated by dividing the estimated group difference by a measure of background variability [standard deviation (SD) of baseline scores].

To assess the equivalence of rTMS and ECT for the primary outcome measure, the end-of-treatment estimate of group difference was transformed into an estimate of group difference in percentage reduction from baseline HRSD and a confidence interval (CI) was then established for this.

The secondary outcomes BDI-II, VAMS and BPRS were analysed using the same ANCOVA-type model as were the subjective side-effects and cognitive measures. Binary outcomes at a single time point (remission at end of treatment or relapse at follow-up) were compared between treatment groups using Fisher's exact tests.

Analyses of economic outcomes measures are discussed.

Economic evaluations

In order to carry out the economic evaluations, data were collected from patients on service utilisation and other dimensions relevant to the measurement of costs using a customised version of the Client Service Recipient Inventory (CSRI).[91] The CSRI has been extensively used in studies of mental health care.[92] The inventory uses information about the service user's background, and comprehensively gathers information about accommodation, and all health, social care and other services used. Through patient interview, data on service use were collected at baseline for the 3-month period prior to entering the study and for the 6-month post-treatment period at follow-up interviews. The CSRI provides a standardised way of recording service use that is also commensurate with accurate cost estimation.

From the completed CSRIs, a full list of services was drawn up to which approximations of the **long-run marginal opportunity cost** of each service were attached. For most services, nationally applicable unit costs at 2003–4 prices were employed, taken from the annual PSSRU compendium.[93] NHS reference costs were used to estimate the cost of inpatient and outpatient attendances. Details of the unit costs used are available from the authors. Direct costs of services in each of the treatment groups were derived by multiplying the frequency and duration of health and social care resources used during the study with the costs of each resource (unit costs).

The unit costs of ECT and rTMS treatment administration were estimated using local data on capital costs (including the treatment suite and machines used during treatment) and cost of professionals' time related to treatment. Capital costs were based on new build and land requirements for an NHS treatment room. This amount was annuitised at a rate of 3.5% over 60 years. The capital cost of equipment was annuitised at 3.5% over 10 years. The profession and grade of the staff involved in the treatment and time they spent on treatment were recorded. These staff included the psychiatrist administering the treatment, anaesthetist, nurse coordinator, operating departmental assistant and ward nurse. Unit costs for these staff were based on 2003–4 estimates taken from Curtis and Netten.[93] The cost of treatment in each of the two groups was then derived by multiplying the number of treatments during the study with the unit cost of treatment administration. Researchers kept information on the number of treatment sessions attended by patients.

Unpaid care within or outside the home by family and other carers was costed using the average hourly rate for a local authority home care worker.[93]

Mean costs were compared using Student's *t*-test and the robustness of the results confirmed using non-parametric bootstrapping techniques to account for any non-normality in their distribution. Data were analysed using SPSS v10 and STATA v8.0 (StataCorp, College Station, TX, USA).

A generic health-related quality of life (HRQoL) measure was employed to generate utility scores for one facet of the economic evaluation. This was not part of the original proposal and was added as a secondary measure following a monitoring visit. The Short Form with 36 Items (SF-36)[94] is one of the most commonly used measures of HRQoL and yields an eight-scale profile of physical functioning, role physical health, bodily pain, general health, vitality, social functioning, role emotional health and mental health well-being scores, in addition to psychometrically based physical and mental health summary measures. QALYs were estimated by combining the time the patient spends in each health state with predicted utility values of the health states. The patient's utility values were derived using SF-36 data.[95] The SF-36 was revised into a six-dimensional health state classification (the so-called SF-6D) and societal weights attached, taken from Brazier and colleagues' work.[95]

The primary economic evaluation was conducted from the perspective of the health and personal social services. We also looked at these service costs plus the costs of informal care. A cost-effectiveness analysis was conducted comparing these comprehensively measured service costs between rTMS and ECT with, first, the difference between the treatments in change in the primary outcome measure (depressive symptoms as measured by the HRSD), and then with the difference between the treatments in QALYs gained. We also looked at cost-effectiveness with and without including the costs of informal care. In each case we planned to compute an incremental cost-effectiveness ratio (ICER) as the mean cost difference between rTMS and ECT divided by the mean difference in change in outcome.

In the event that one treatment was both more effective and more costly than the other, the

decision-maker would need to consider whether it is worth incurring the higher costs in order to achieve the improved outcomes. The standard approach now employed by health economists to reveal the nature of these trade-offs – and to represent the inherent uncertainty in any evaluation – is to plot a cost-effectiveness acceptability curve (CEAC).[96,97] We did so for each cost–outcome combination.

The CEAC reveals to the decision-maker what the probability is of rTMS being seen as cost-effective relative to ECT given different (implicit monetary) values placed on incremental outcome improvements. In the present study, for each different value attached to a one-point improvement in the HRSD or for each QALY gained, we calculated this probability. The CEAC also represents uncertainty in the estimation of the ICER, including in circumstances where statistical power limits significance testing[98] and also where one wants to understand the sensitivity of the results to key assumptions made in the analysis. Lack of statistical power is a common problem in economic evaluations, especially in the mental health area.[99] Moreover, in a decision-making context it could be argued to be perverse to reject an intervention with the highest probability of being cost-effective because of the limitations of conventional hypothesis testing.[100] Bootstrap analyses were used to draw 1000 repeat samples from the data and the CEAC generated by plotting the proportion of ICERs that were cost-effective for a range of willingness to pay values. The bootstrap approach also allows for possible skewness in the cost variable.[101,102]

Chapter 4
Results

Participant flow and follow-up

The trial profile is shown in *Figure 1*. Of 260 patients referred for ECT, 107 were depressed patients eligible to enter the trial. The most common reason for exclusion was being formally treated in accordance with the UK Mental Health Act 1983 while not consenting to ECT. Of the eligible patients, 46 (43%) consented to enter the study. There was no statistical difference in mean age or sex ratio between eligible patients who consented to enter the trial and those who declined to participate. Five patients in the rTMS group terminated treatment early, having ⩽10 sessions, because they felt no improvement, and one patient could not attend the fifteenth session; all but one of these agreed to end-of-treatment assessments. The rTMS treatments were well tolerated and nobody dropped out because of pain or discomfort at the stimulation site. None of the ECT patients dropped out at this stage of the trial.

In the ECT group, 18 (81.8%) had bilateral and four (18.2%) had unilateral ECT. The mean (standard deviation) number of rTMS sessions was 13.7 (2.7) and the mean number of ECT sessions was 6.3 (2.5) (range 2–10). Although the number of sessions differed between the two treatment groups, the durations (total number of days from first to last treatment) of the treatment courses were comparable [ECT, 22.4 (12.7); rTMS, 19.5 (6.3)]. Four patients in the rTMS group crossed over to have ECT after the end-of-treatment assessments but were analysed in the group to which they were randomised.

It proved impossible to keep assessors blind to treatment allocation. Rater treatment guesses were not available for eight patients. Of the remaining 38 patients, five had directly informed raters about their treatment and raters guessed allocated treatment correctly for 30 patients (92%). Patient demographic and clinical baseline information is summarised in *Table 1*. This shows that the randomisation reasonably balanced the treatment arms with respect to potential confounders.

Response to treatment

Changes in the HRSD scores over time in the two treatment arms are shown in *Figure 2*. The post-treatment group difference varied significantly with assessment time point [group × time interaction: $t = -2.49$, degrees of freedom (df) = 45, $p = 0.017$]. *Post hoc* tests demonstrated that the end-of-treatment HRSD scores were significantly lower in the ECT group than the rTMS group ($t = 3.3$, df = 45, 95% CI 3.40 to 14.05, $p = 0.002$), demonstrating a strong standardised effect size of 1.44. However, at 6 months' follow-up, HRSD scores did not differ between the two groups ($t = -0.09$, $df = 45$, 95% CI –6.92 to 6.33, $p = 0.93$). At end of treatment, 13 patients (59%) in the ECT group met the remission criterion (HRSD ⩽8) whereas only four (17%) did so in the rTMS group (Fisher's exact test, $p = 0.005$).

In addition to the intention-to-treat analysis, and as a sensitivity analysis, a *post hoc* received treatment analysis was performed. However, this did not affect the primary outcome. This analysis excluded the five patients in the rTMS group who had ⩽10 rTMS sessions, and took into account the crossover of five rTMS patients to the ECT group before the 6-month follow-up assessment.

The mean reduction in HRSD score achieved at end of treatment from adjusted baseline score was 14.1 for ECT and 5.4 for rTMS. This translates into mean percentage reductions from baseline of 58% for ECT and 22% for rTMS. Thus the absolute difference in percentage reduction from baseline was 36% (95% CI 14 to 58%). This point estimate lies well outside the predefined equivalence range (i.e. up to 18.1 percentage points), as does almost all the respective CI with just a small fraction of the confidence range (from 14 to 18.1%) falling into the predefined equivalence range. The rTMS treatment effect was therefore statistically significantly worse than that of ECT and it was at least 14 percentage points worse.

Changes for the BDI-II, VAMS and BPRS scores are shown in *Figure 3*. Although these showed

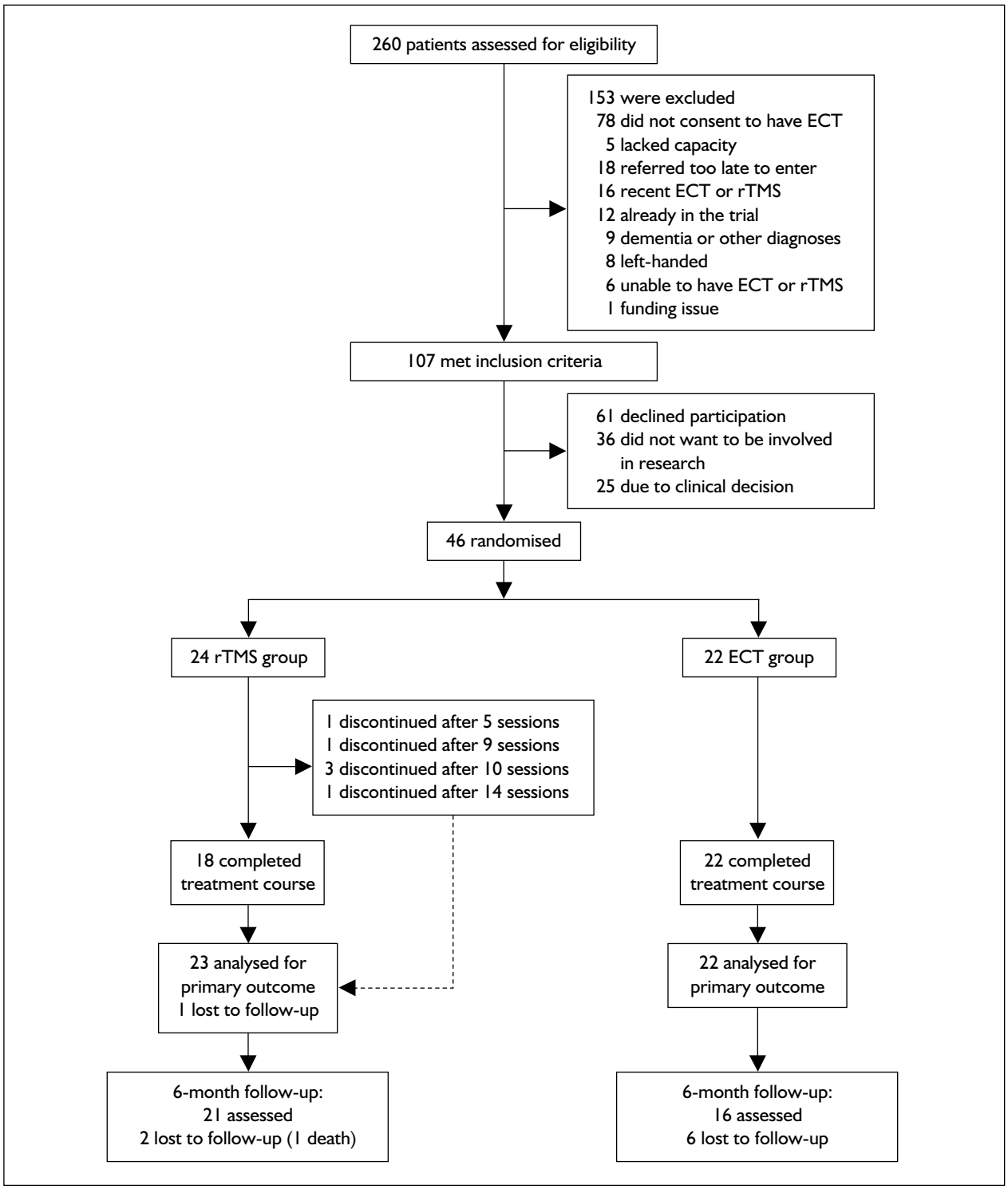

FIGURE 1 *Trial profile*

similar patterns to the HRSD scores, there was no statistical evidence for any of these secondary outcomes that the treatment effect varied over time (group × time interaction: BDI-II, $t = -1.2$, $df = 45$, $p = 0.25$; VAMS, $t = -1.3$, $df = 41$, $p = 0.20$; BPRS, $t = -0.85$, $df = 43$, $p = 0.40$). The interaction terms were therefore excluded from the model and the main effect of treatment arm evaluated across the end-of-treatment and 6-month follow-up time points. This showed significantly lower scores in the ECT group compared with rTMS on the BDI-II ($t = 2.7$, $df = 45$, 95% CI 2.3 to 15.6, $p = 0.01$), VAMS ($t = 4.2$, $df = 41$, 95% CI 106.5 to 302.8,

TABLE 1 *Baseline characteristics*

	rTMS group[a] (*n* = 24)	ECT group[a] (*n* = 22)
Age (years)	63.6 (17.3)	68.3 (13.4)
Female	16 (67.7%)	16 (72.7%)
Inpatient	15 (62.5%)	15 (68.2%)
Patients with bipolar depression	2 (8.3%)	2 (9.1%)
Level of treatment resistance	2.4 (1.0)	2.5 (1.4)
Median duration (months) of depressive episode (range)	7.7 (0.6–24.0)	6.1 (1.4–24.0)
Number of previous depressive episodes	3.7 (2.3)	4.2 (2.6)
Previous history of ECT	15 (62.5%)	12 (54.5%)
Number of psychotropic medications per patient	1.7 (1.2)	1.7 (1.2)
Number of patients on psychotropic medications:		
SSRI	6 (25%)	5 (22.7%)
TCA	2 (8.3%)	2 (9.1%)
Venlafaxine	10 (41.7%)	7 (31.8%)
Mirtazapine	4 (16.7%)	5 (22.7%)
Lithium	5 (20.8%)	6 (27.3%)
Anticonvulsant	2 (8.3%)	3 (13.6%)
Benzodiazepines	2 (8.3%)	5 (22.7%)
Antipsychotics	7 (29.2%)	7 (31.8%)
Zopiclone	6 (25%)	3 (13.6%)
L-Tryptophan	1 (4.2%)	0 (0%)
Patients with psychosis	4 (16.7%)	3 (13.6%)
HRSD score	23.9 (7.0)	24.8 (5.0)
BDI-II score	36 (8.7)	37.8 (10.5)
VAMS aggregate score	489.0 (119.8)	572.1 (94.9)
BPRS score	36.8 (8.2)	36.4 (8.3)
SF-36 mental health component score	48.9 (12.6)	42.7 (7.5)

SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
[a] Data are mean (SD) or number (%) of patients, unless indicated otherwise.

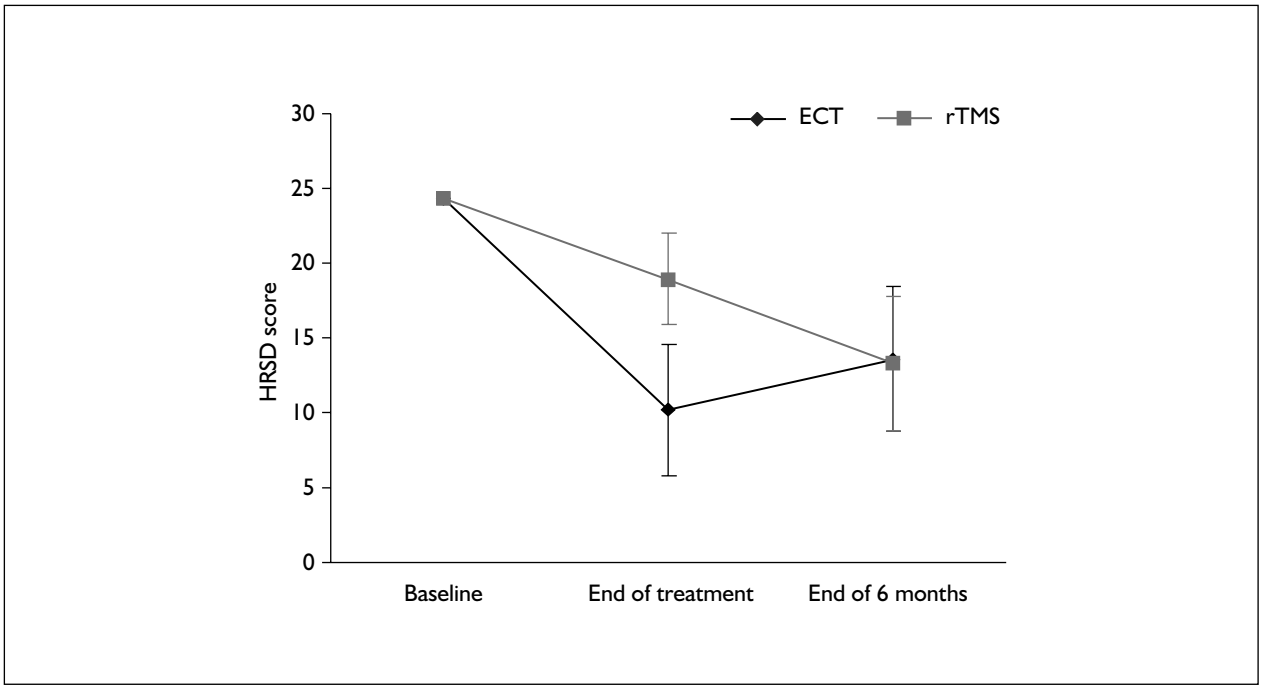

FIGURE 2 *Mean HRSD score. The graph shows predicted mean scores per treatment arm and post-treatment time points, adjusted to sample average baseline values, with 95% CIs.*

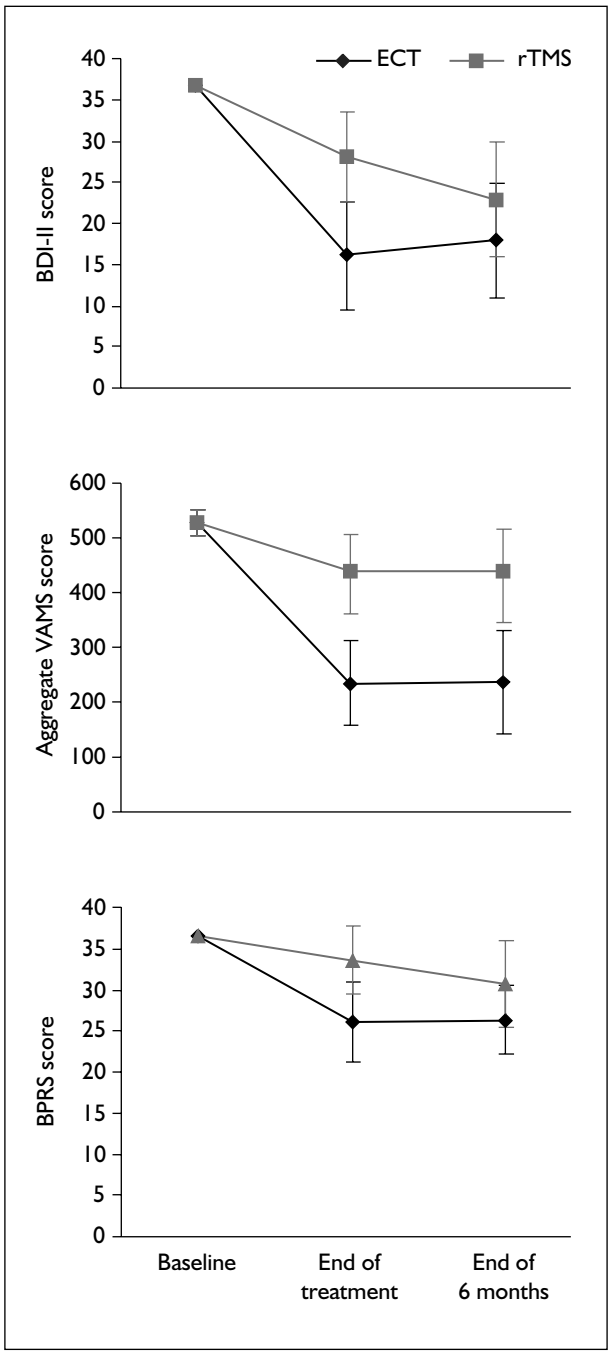

FIGURE 3 *Mean BDI-II, aggregate VAMS and BPRS scores. The graphs show predicted mean scores per treatment arm and post-treatment time points, adjusted to sample average baseline values, with 95% CIs.*

$p < 0.001$) and BPRS ($t = 2.2$, $df = 43$, 95% CI 0.05 to 11.7, $p = 0.03$). All ECT reductions translated into substantial effects sizes on the standardised scale (BDI-II, 0.9; VAMS, 1.8; BPRS, 0.7). Six-month follow-up data were available for 12 of the 13 ECT remitters and five (42%) of these met the criterion for relapse (HRSD ⩾12) whereas two (50%) did so in the rTMS group (Fisher's exact test for comparing proportions: $p = 1$).

Subjective and objective side-effects

Subjective side-effects

Change over time for the CSSES score is shown in *Figure 4* and *Table 2*. The ECT group had a significantly lower subjective side-effect score at end of treatment ($t = 2.45$, $df = 40$, 95% CI 0.51 to 5.33, $p = 0.02$). CSSES scores at baseline were significantly correlated with the HRSD scores (Spearman correlation $r = 0.439$, $p = 0.003$). Change in HRSD score from baseline to end of treatment was also strongly correlated with change in CSSES score (Spearman correlation $r = 0.762$, $p < 0.001$). The self-reported cognitive subscores from the CSSES were analysed separately and results are shown in *Table 2*; there was no significant difference over time or between groups.

Objective side-effects

Table 3 shows results derived from the CAMCOG cognitive examination. No significant differences were found, either between the ECT and rTMS groups or over time, for total CAMCOG and MMSE scores or for subscores on verbal fluency or anterograde and retrograde memory. There was a significant group effect for the attention and orientation subscore ($t = -3.06$, $df = 36$, 95% CI –3.9 to –0.8, $p = 0.004$), with the ECT group showing mild improvement at the end of treatment, in contrast to the rTMS group, where the score had decreased.

Unfortunately, the completion rates for the other neuropsychological tests and for the AMI were too low and insufficient to allow for analysis. A 76-year-old man in the rTMS group died from previously diagnosed prostatic cancer during the 6-month follow-up period. No other major adverse events were recorded, such as seizure induction with rTMS or anaesthetic complications with ECT, and mania was not induced in any patients during the study.

Economic analyses

Table 4 gives the proportion of patients in each of the groups using health and community-based services 6 months after treatment. At 6-month follow-up, service use data were collected on 28 patients (10 in the ECT group and 18 in the rTMS group). A wide range of services were used, delivered by a range of local authority, NHS and voluntary sector organisations. Although moderate use was made of all services, patients made greater contact with NHS services and use of social care services, especially that of the social worker.

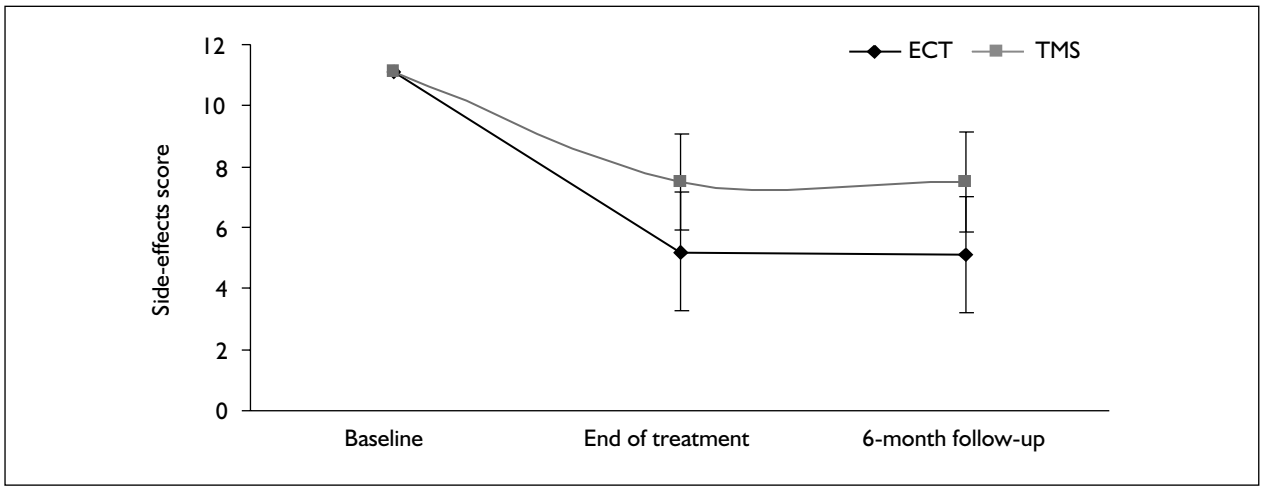

FIGURE 4 *Mean CSSES scores. The graph shows predicted mean scores per treatment arm and post-treatment time points, adjusted to sample average baseline values, with 95% CIs.*

TABLE 2 *Subjective symptoms/side-effects as measured by the CSSES*

	ECT group[a] (*n* = 20)			rTMS group[a] (*n* = 23)			Statistical analysis		
	Baseline	End of treatment	6-month assessment	Baseline	End of treatment	6-month assessment	Group × time interaction	Group effect	Time effect
Symptom/ side-effects score	14.2 (4.7)	6.7 (6.4)	7.1 (4.7)	13.2 (5.8)	9.7 (4.6)	8.9 (4.7)	$t = -0.70$ $p = 0.49$	$t = 2.45$ $p = 0.02$	$t = -0.09$ $p = 0.93$
Cognitive subscore	2.4 (1.2)	1.5 (1.4)	1.2 (1.4)	2.1 (1.3)	1.5 (1.2)	2.1 (1.5)	$t = 1.43$ $p = 0.16$	$t = 1.69$ $p = 0.10$	$t = 0.81$ $p = 0.42$

[a] Data are mean (SD).

Table 5 summarises the number of hours of carer inputs in the 6-month follow-up period. The table distinguishes personal care, child care, help in and around the home and help outside the home. The total caregiver input was lower after treatment (11 hours per week for ECT patients and 16 hours per week for rTMS patients) than at baseline (19 hours per week for ECT patients and 23 hours per week for rTMS patients).

Patients treated with ECT received a wider range of professional input than those treated with rTMS. A summary of the non-capital resources used during treatment is shown in *Table 6*. It costs the NHS £211 per administration of ECT; 69% of this cost is related to the professional input and the remainder is related to capital. The cost per session of rTMS was lower than that of ECT. Over the study period, the mean cost of rTMS treatment of £1444 (SD £286) was not significantly higher than the mean cost of ECT at £1314 (SD £525).

The intensity of use of each of the services (*Table 5*) was weighted by its unit cost to give the total cost of service-based inputs at 6-month follow-up. The costs of all services (both formal and informal) used after treatment are shown in *Table 7*. NHS, non-NHS and informal care costs were similar between the groups, but informal care costs were higher for the rTMS group (£2795; $p = 0.04$) and contributed substantially to the total cost for this group.

In order to examine the responsiveness of costs to changes in different variables, sensitivity analyses were performed. The effects of the two scenarios on the total mean NHS costs and total costs were assessed (*Table 7*). The scenarios were (a) varying the unit cost of informal care to the average gross hourly wage for an adult (£11.47) and (b) varying the unit cost of informal care to costs based on the minimum hourly wage (£4.85). Under all scenarios, there were marginal changes in mean total costs.

TABLE 3 *CAMCOG assessment and subscores*

	ECT group[a] (*n* = 16)			rTMS group[a] (*n* = 22)			Statistical analysis		
	Baseline	End of treatment	6-month assessment	Baseline	End of treatment	6-month assessment	Group × time interaction	Group effect	Time effect
CAMCOG (max. = 106)	83.2 (11.1)	87 (14.8)	86.1 (17.3)	85.3 (11.3)	84.7 (17.4)	84.8 (14.5)	$t = 0.54$ $p = 0.62$	$t = -1.86$ $p = 0.07$	$t = 1.10$ $p = 0.28$
MMSE (max. = 30)	24.3 (3.6)	25.6 (3.9)	25.4 (5.3)	25.7 (3.9)	24.4 (5.3)	24.7 (4.8)	$t = -0.14$ $p = 0.89$	$t = -1.77$ $p = 0.08$	$t = 0.75$ $p = 0.46$
Attention and orientation (max. = 17)	12.8 (3.2)	13.9 (3.6)	13.9 (3.5)	14.7 (3.0)	13.5 (3.3)	13.4 (3.8)	$t = -0.49$ $p = 0.63$	$t = -3.06$ $p = 0.004$	$t = 1.15$ $p = 0.26$
Verbal fluency[b]	12.8 (7.1)	14.0 (6.0)	12.6 (8.1)	15.8 (4.1)	16.6 (6.4)	17.0 (5.9)	$t = -0.06$ $p = 0.96$	$t = -0.01$ $p = 0.99$	$t = 0.21$ $p = 0.83$
Anterograde memory (max. = 20)	15.1 (2.9)	16.9 (2.0)	16.5 (1.8)	14.2 (3.6)	15.3 (3.9)	15.1 (3.2)	$t = -0.03$ $p = 0.98$	$t = -1.22$ $p = 0.23$	$t = -0.20$ $p = 0.84$
Retrograde memory (max. = 10)	7.7 (1.9)	7.4 (2.6)	6.9 (2.8)	7.2 (2.3)	6.9 (2.7)	6.6 (2.7)	$t = 0.82$ $p = 0.42$	$t = -0.76$ $p = 0.45$	$t = 0.32$ $p = 0.75$

[a] Data are mean (SD).
[b] Number of animals named in 1 minute.

TABLE 4 *Services used 6 months after treatment: resources used over 3-month period*

	ECT group (*n* = 10)		rTMS group (*n* = 18)	
	No. using	Mean[a]	No. using	Mean[a]
Hospital-based care				
Inpatient (bed day)	1	25	5	21
Outpatient (attendance)[b]	3	1	7	6
Accident and emergency (attendance)	1	1	2	1
Day hospital (contact)	1	1	–[d]	–
Community-based care				
Day services (day)	1	1	1	1
Lunch club (visit)	1	7	–	–
Social club (visit)	1	25	–	–
District nurse (contact)	1	2	2	4
GP (contact)	5	2	12	6
Practice nurse (contact)	1	1	2	1
Community psychiatrist (contact)	1	1	7	4
Community psychiatric nurse (contact)	2	5	6	11
Social worker (contact)	2	7	3	7
Psychologist (contact)	1	6	3	6
Other community-based professional (contact)[c]	7	2	6	2

[a] Mean calculation based on users of relevant service only, not across full sample. The unit of measurement is shown in brackets.
[b] Includes outpatient attendances for specialist services (diabetic clinic, X-ray, urine test, psychiatry).
[c] Includes dentist, optician and home treatment team.
[d] Dashes indicate no use made of service.

TABLE 5 *Care giver input by treatment group*

	Baseline		6-month follow-up	
	ECT group	**rTMS group**	**ECT group**	**rTMS group**
Child care – number receiving care	–	2	–	2
Child care – hours per week[a]	–	32 (40)	–	17 (16)
Personal care – number receiving care	–	1	2	3
Personal care – hours per week[a]	–	7 (–)	5 (4)	4 (2)
Help in and around home – number receiving care	9	8	1	8
Help in and around home – hours per week[a]	12 (12)	13 (10)	8 (0)	14 (6)
Help outside home – number receiving care	8	7	2	10
Help outside home – hours per week[a]	10 (8)	7 (5)	2 (0)	5 (4)
Total caregiver input (hours per week)[a]	19 (19)	23 (18)	11 (2)	16 (13)

[a] Data are shown as mean hours (SD) for those who received help only.

TABLE 6 *Non-capital treatment resources for ECT and patients*

Resource use	**ECT group**	**rTMS group**
Mean time spent in treatment	60 minutes	22 minutes 20 seconds
Mean number of treatment administrations	(n = 22)	(n = 24)
(SD)	6 (2)	14 (4)
Professionals:	**Average time spent in treatment (minutes)**	**Average time spent in treatment (minutes)**
Consultant psychiatrist	45	25
Anaesthetist	45	NA
Operating departmental assistant	60	NA
Nurse coordinator	60	NA
Ward nurse	60	35[a]

NA, not applicable.
[a] Only applicable to rTMS patients who were inpatients.

TABLE 7 *Mean total costs at 6-month follow-up*

	Mean cost (SD) (£)		Mean difference ECT – rTMS	*p*-Value	95% CI
	ECT group	**rTMS group**			
Cost category					
Treatment cost[a]	1314 (525)	1444 (286)	–130	0.31	–387 to +127
NHS cost	1245 (2962)	2922 (256)	–1677	0.29	–4866 to +1511
Non-NHS cost	450 (994)	65 (256)	385	0.13	–117 to +888
Total NHS and non-NHS cost	1695 (3002)	2987 (4426)	–1292	0.42	–4527 to +1943
Treatment costs plus 6-month follow-up NHS and non-NHS cost	2834 (3097)	4441 (4477)	–1607	0.28	–4575 to +1316
Informal care	335 (1060)	2795 (3583)	–2460	0.04	–4862 to –57
Total cost including informal care costs	3169 (3261)	7236 (7157)	–4067	0.05	–8136 to +2
Sensitivity analysis: effect on mean total costs under alternative assumptions					
Scenario 1: Informal care cost based on average gross hourly earnings (£11.47)	3133 (3226)	6927 (6819)	–3794	0.06	–7710 to +122
Scenario 2: Informal care cost based on minimum wage (£4.85)	2992 (3105)	5510 (5356)	–2518	0.13	–5806+770

[a] Treatment costs are estimated based on a sample of 22 patients in the ECT group and 24 patients in the rTMS group. All other costs are based on sample sizes of 10 and 18 for the ECT and rTMS groups, respectively.

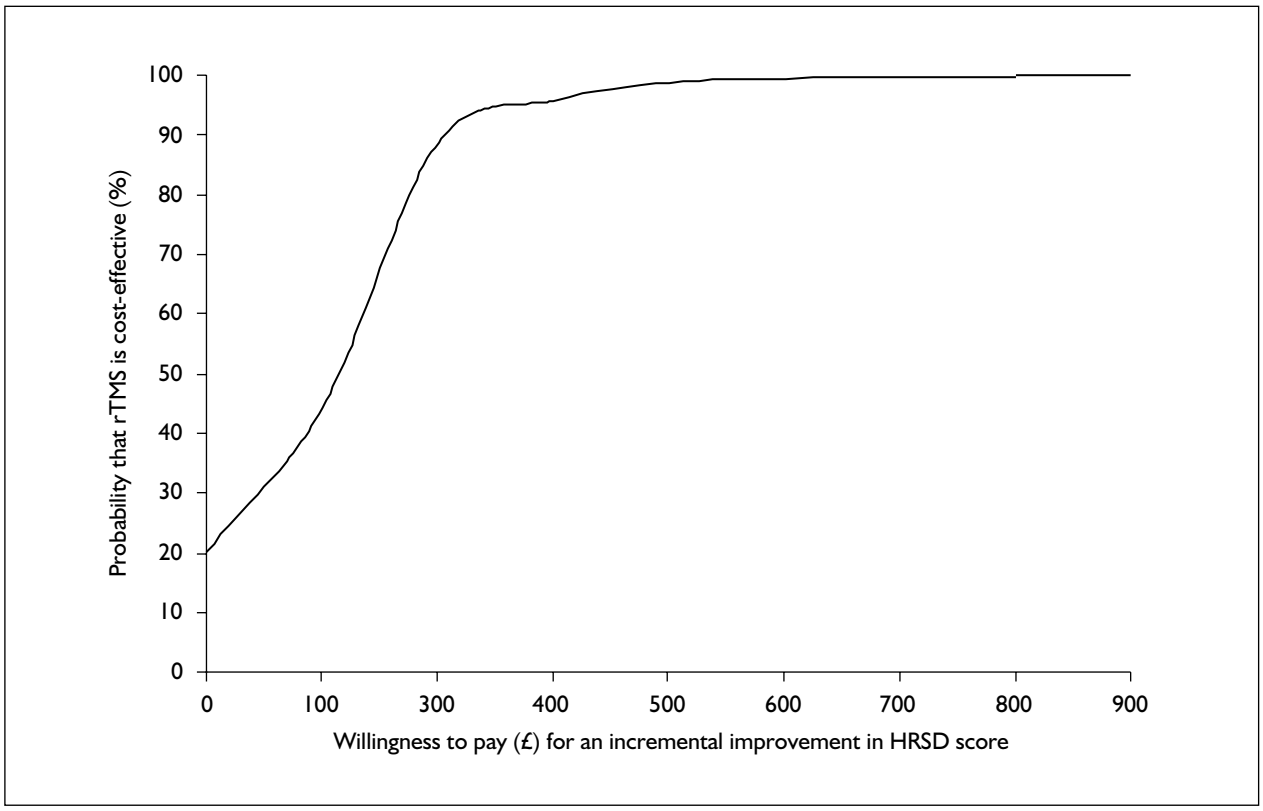

FIGURE 5 *CEAC – probability that rTMS is cost-effective as a function of the decision-makers' critical cost-effectiveness ratio*

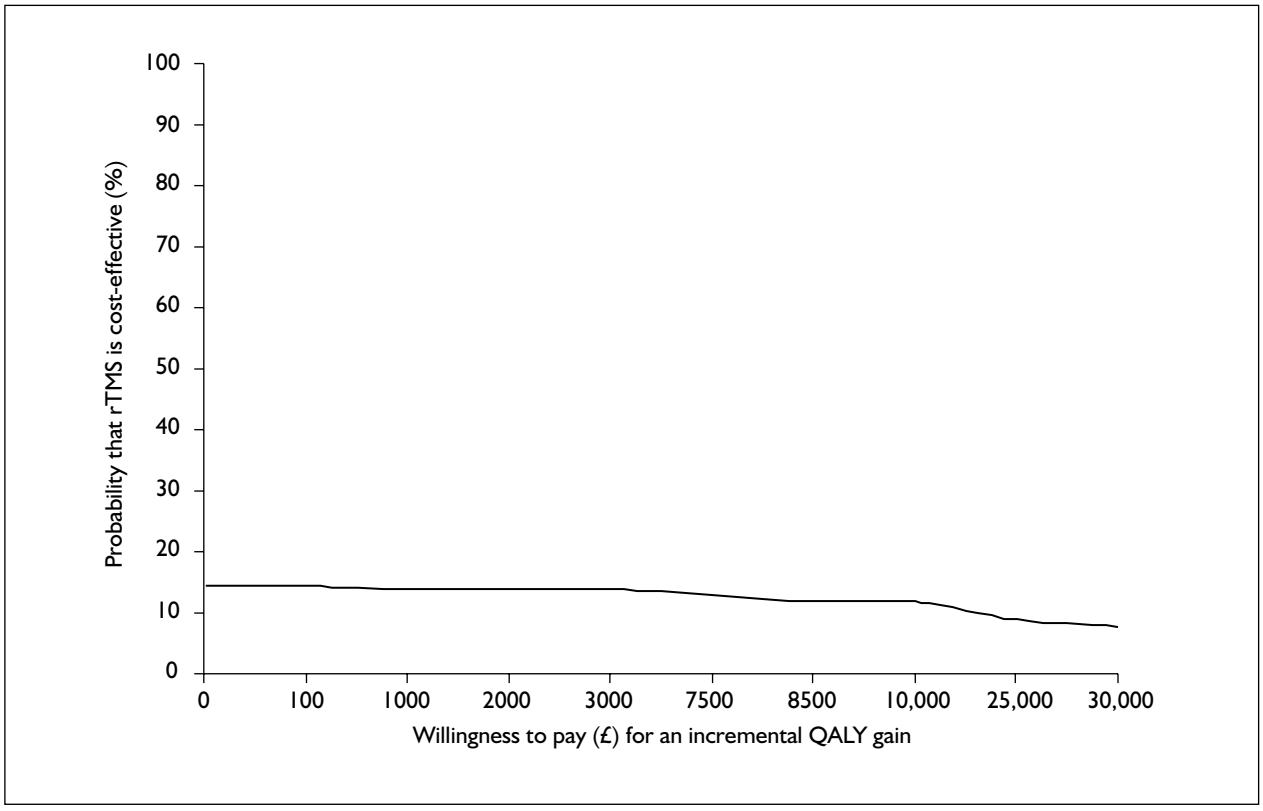

FIGURE 6 *CEAC – probability that rTMS is cost-effective as a function of the decision-makers' critical cost-effectiveness ratio*

The average length of time spent in at least one category of care giving was 16 hours per week. When the gross hourly wage for an adult was used, as an estimate of the unit cost of care giving, the mean difference in total costs decreased by £273. Under a more conservative estimate of the hourly cost of care giving of £4.85, the difference in the total costs was £1549. However, these differences remained non-significant.

The primary measure of cost-effectiveness was the incremental cost per change in HRSD over the full study period (29 weeks). The secondary analysis was the incremental cost per QALY gained over the same period. It was not necessary (indeed not possible) to calculate ICERs since there were no significant differences in costs and effects on the primary outcome measure. However, there is uncertainty around these results. The development of more sophisticated tools to measure and represent cost-effectiveness has followed criticisms of decision-making purely on the basis of statistical inference. Instead, a Bayesian decision-making approach has been advocated: available data on costs and effects are used to plot a CEAC. The CEAC for rTMS compared with ECT for the primary outcome (HRSD) is shown in *Figure 5*. If society were willing to pay nothing for an improvement in depressive symptoms, there is a 20% probability that rTMS would be seen as a cost-saving choice compared with ECT. If, however, society is willing to pay £500 for each unit improvement in depressive symptoms for each person (as measured by the HRSD), there is a 99% probability that rTMS would be viewed as cost-effective compared with ECT. By all sensible criteria this would seem a very considerable amount to pay for such a minor change in symptoms.

Patients responded much better to ECT than to rTMS by the end of the allocated treatment course. However, over the 6-month follow-up period ECT patients had a mean QALY gain of 0.0297 (0.056) and rTMS patients had a mean QALY gain of 0.0300 (0.053). The differential QALY gain of treatment with rTMS over ECT was 0.0003 ($p = 0.987$). This suggests that treatment by rTMS does not provide any additional gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months. In terms of cost-effectiveness, at values of willingness to pay up to £30,000 per QALY gained, the probability of cost-effectiveness was 14% (*Figure 6*). Hence, the findings suggest that rTMS has a very low probability of being seen as a cost-effective alternative to ECT for treatment-resistant depression.

Chapter 5
Discussion

The antidepressant effects of ECT and rTMS

This trial showed that ECT is a substantially more effective treatment for severe depression than 3 weeks of rTMS as administered in this study. It would have been ethically unjustifiable to have a placebo group due to the severity of depression in the trial participants. However, it is noteworthy that similar treatment effects were found on all outcome measures. Interestingly, the HRSD scores in the rTMS group improved during the 6-month follow-up period and became similar to those in the ECT group, probably due to ongoing intensive management as reflected in the continuing high costs. Indeed, as previously mentioned, four patients in the rTMS group went on to be treated with ECT.

Rater blinding was clearly not maintained. This was probably due to obvious differences between the treatments and patients inadvertently divulging details. Loss of rater blinding is a potential source of bias, particularly for our primary outcome – the observer-rated HRSD. However, we found similar end-of-treatment results with the self-rated BDI-II and VAMS.

This pragmatic trial attempted to reflect usual medical practice. Patients continued on their usual medications, including benzodiazepines and anti-epileptic mood stabilisers, which could interfere with both ECT and rTMS treatments. Recruitment was slow and the numbers enrolled relatively small, reflecting the difficulties inherent in clinical trials involving patients with severe depression. However, the most common reason for not entering the trial was not consenting to have ECT; such patients were being treated under Section 58 of the Mental Health Act 1983 (see *Figure 1*). As rTMS requires a high degree of cooperation, it would not have been possible to administer it to these patients without their full cooperation. In addition, there was no significant difference between eligible patients who agreed to participate and those who declined with regard to age and sex ratio. Hence the trial reflects the population referred for ECT whom it was possible to treat with rTMS and as such the results are generalisable to this patient population. Loss to follow-up at 6 months was greater in the ECT group (27% versus 12.5%); the main reason for both groups was unwillingness to participate any more in research.

Previous randomised comparisons of rTMS and ECT have found rTMS to be either less effective than[61,62] or not statistically significantly different from ECT.[63,64] These studies are methodologically variable, not powered and most have small sample sizes. In the best designed study, Grunhaus and colleagues[64] allocated 20 patients to right unilateral ECT [stimulus dosing protocol using 2.5 times the ST; mean number of treatments = 10.3 (3.1); seven patients switched to bilateral ECT when after six treatments their HRSD score did not decrease by ⩾30%] and 20 patients to rTMS (20 daily sessions of 20 trains of 90% of MT at 10 Hz for 6 seconds, i.e. 1200 pulses per day). They found the same remission rate (HRSD ⩽8) of 30% in both the ECT and rTMS groups. Although the baseline HRSD scores were very similar to those reported in our trial, this remission rate for ECT is nearly half that (59.1%) found in our study, using the same criterion. It is possible that this form of unilateral ECT was less effective, as has been previously reported,[25] accounting for the apparent equivalence in treatments. In our trial, five of 12 (42%) ECT remitters met the relapse criterion (HRSD ⩾12) at 6 months. In previous randomised studies of rTMS and ECT, 20% of responders to ECT (i.e. end-of-treatment HRSD ⩽10) were deemed to have relapsed (HRSD ⩾16) after 6 months.[65] Using these less stringent criteria, the relapse rate for ECT responders (n = 14) in our study remains unchanged.

It could be suggested that for rTMS to be as effective as ECT, many more weeks of high-intensity treatment would have been required.[103] However, it has previously been reported that little further benefit appears to be derived in continuing rTMS in patients with minimal improvement after 2 weeks of rTMS.[61] In our study, five patients decided to stop the rTMS course early due to a perceived lack of benefit. In the remaining 19 patients who received 3 weeks of rTMS, the mean HRSD score declined only 19.7 (32.5)% from baseline. For this trial rTMS stimulus parameters were chosen that were more intensive than

previously published in the hope of achieving greater efficacy. In addition, the mean durations of rTMS and ECT courses were similar, allowing for time-dependent comparison. A recent meta-analysis of trials of real versus placebo rTMS for treating depression concluded that there was currently insufficient evidence to support its routine use but that it did merit further investigation.[56] We recommend that rTMS parameters (e.g. coil placement, stimulus intensity, number of treatments) be more rigorously characterised before patients are treated with even longer treatment courses.

Side-effects

This is the first report of side-effects in a randomised trial of ECT and rTMS. There is evidence that some of the putative side-effects of ECT are possibly symptoms of depression.[74,104] Our findings support this. There was a strong correlation between baseline HRSD scores and baseline CSSES symptom scores and also between change in HRSD and CSSES scores. The ECT group, which experienced significantly greater improvement in depressive symptoms, also experienced lower side-effects scores post-treatment than the rTMS group. Interestingly, there was a slight reduction (although not statistically significant) in reported cognitive complaints at end of treatment for both groups, with the two groups having similar CSSES cognitive subscores. This contrasts with a recent non-randomised comparison of rTMS and ECT that found that subjective memory complaints were unchanged from baseline in the ECT group whereas the rTMS group had fewer memory complaints than at baseline.[105] In that study, ECT patients had measurable memory deficits post-treatment whereas the rTMS group did not.

It is well established that depression is often associated with poor memory and concentration.[82] This is certainly borne out by the baseline scores in the present study, with patients in both groups having evidence of cognitive deficits. Previous studies have shown that ECT can adversely affect cognition. It can interfere with memory, disrupting new learning[106] and causing impairment in remote memory.[24] In contrast, studies on rTMS have suggested either no adverse effects on cognitive performance[107] or indeed some positive effects independent of improved mood.[108]

Two previous randomised trials comparing rTMS and ECT used the MMSE to assess global cognition but did not find differences either between the treatment groups or over time.[61,64] We used a more detailed cognitive assessment instrument but also did not find differences in cognitive performance either between the two treatment groups or over time. We did not detect measurable adverse effects on cognition induced by ECT in the present study. However, neither group's cognitive performance was enhanced as mood improved. The only subtest scores to show a statistically significant difference between the groups was attention and orientation, which improved slightly in the ECT group but not in the rTMS group. The reasons for this are unclear but could reflect enhanced concentration being a sensitive indicator of improved mood. It may be that the CAMCOG interview schedule, originally designed for the diagnosis of dementia, is not a sufficiently sensitive instrument to detect subtle cognitive changes induced by either ECT or rTMS. We attempted additionally to perform more detailed neuropsychological testing, including testing of autobiographical memory, but a high proportion of patients could not complete these tests and we were unable to derive any conclusions from them. However, it is an encouraging finding that ECT did not produce a deterioration in any cognitive measure examined and on some measures there was a trend towards improvement.

None the less, caution is warranted in interpreting these cognitive findings in the light of the high drop-out rate and small sample size. With a larger sample size and a primary focus on cognitive outcome measures, especially retrograde memory, it may be that significant changes in cognition could be demonstrated, including improvements on some cognitive measures as mood improves. Finally, both ECT and rTMS were well tolerated and it is reassuring that no patient dropped out of either treatment because of adverse side-effects.

Economic evaluations

Resources for healthcare are almost always scarce relative to needs or wants, and the purpose of an economic evaluation is to inform the choices that a decision-maker faces in these circumstances. The economic evaluation might even provide an argument for increasing expenditure on services for people with depression in circumstances where the benefits in terms of improved health status and quality of life are substantial. This study included an investigation of the resource implications and cost-effectiveness of rTMS compared with ECT.

The cost of a single session of rTMS was lower than the cost of a session of ECT. Patients receiving rTMS had more treatment sessions, however, and direct treatment costs were not significantly higher. Health and social care service costs were also not significantly different between the groups, but the costs associated with the unpaid inputs of family and other carers were much higher for the rTMS group. Overall, the sum of formal and informal care costs during the 6-month follow-up period were £5782 for the rTMS group (equivalent to £222 per week) and £2030 for the ECT group (or £78 per week). These findings are consistent with previous cost-of-illness research suggesting that depression is associated with high use of health services,[109] and with previous randomised trials of antidepressants that have similarly found high and continuing health services use patterns.[110]

ECT has been reported to be associated with improved quality of life that is evident within the first month post-treatment and that can be maintained for up to 1 year.[66,67] In this study, HRQoL was measured using the SF-36, from which it was possible to calculate measures of QALYs (using the SF-36 approach of Brazier and colleagues).[95] No relative QALY gains were found for either treatment over the other.

There are now numerous economic evaluations of depression treatment, but very few previous studies of the cost-effectiveness of either ECT or rTMS.[111] A recent attempt to generate a model proved inconclusive, mainly due to a lack of suitable randomised controlled trial data and uncertainty around the optimal treatment parameters for ECT.[68] A published decision analytical model of the cost-effectiveness of rTMS suggested that it would be cost-effective compared with ECT alone.[69] In contrast, this randomised controlled trial has found that rTMS has a low probability of being more cost-effective than ECT. Indeed, when considering the cost of achieving a QALY gain, the cost-effectiveness of rTMS does not look attractive by reference to the threshold revealed by a review and econometric analysis of recommendations made by NICE. This review found an implicit threshold of somewhere between £30,000 and £40,000 per QALY gained, although the figure or range does vary depending on a number of factors.[112]

Chapter 6
Conclusions

Implications for the NHS

We have carried out a randomised controlled trial of ECT and rTMS within a defined NHS catchment area population. To our knowledge, this is the first randomised trial involving ECT to be carried out in the UK since the mid-1980s and the first in the UK to report outcomes with contemporary ECT practice using a stimulus dosing protocol. The evidence confirms the clinical effectiveness of ECT for treating major depressive episodes and indicates that 3 weeks of rTMS as administered in this study is not equivalent to ECT. In addition, the evidence suggests that such courses of rTMS would not be cost-effective.

Whether the effectiveness of rTMS as an antidepressant can be improved by identifying optimal treatment parameters remains to be established. The trial results do not support the use of rTMS outside a research setting. However, it is clear that ECT is a powerful antidepressant treatment and what is now required for ECT is to refine the technique further such that side-effects are reduced but its superior effectiveness is maintained.

Recommendations for further research

All the patients randomised to ECT in this study received brief pulse treatment and the majority were given bilateral ECT at 1.5 × ST. Brief pulse bilateral ECT appears to be the most commonly used form of ECT in the UK when compared, for example, with unilateral ECT. However, there is emerging evidence that high-dose unilateral ECT (e.g. at 4–6 × ST) may be as effective as standard bilateral ECT but is associated with less cognitive side-effects. It is possible that further reducing the pulse width of the electrical stimulus in ECT may also be associated with less side-effects and it has been suggested that it may be possible to disassociate the therapeutic effects of ECT from its cognitive side-effects. There is therefore a need for large-scale, adequately powered randomised controlled trials comparing different forms of ECT, e.g. bilateral ECT, high-dose unilateral ECT and high-dose ultra-brief pulse unilateral ECT, using simple but sensitive measures for both effectiveness and cognitive side-effects.

The low therapeutic response to the course of rTMS used in this study was disappointing. Although the protocol used was more intensive and prolonged than many previous studies, one possibility was that the treatment protocol was sub-optimal. However, the current evidence base for the effectiveness of rTMS for depression is limited and potentially optimal treatment parameters have not yet been established. Therefore, before any further trials to compare rTMS with established antidepressant treatments, the next generation of randomised trials of rTMS should 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.

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Contribution of authors

All authors listed below were involved in either the conception and design of the study or its analysis and interpretation. All authors were involved in drafting the report and approved the final version. Declan M McLoughlin (Senior Lecturer) conceived and designed the study and is its overall guarantor. Denzil Edwards (Research Psychologist), Michael Philpot (Consultant Psychiatrist), Richard Brown (Professor of Psychology), Robert Howard (Professor of Old Age Psychiatry), Sabine Landau (Head of Department of Biostatistics and Computing) and Sophia Rabe-Heskith (Reader in Statistics) contributed to the original design, with particular contributions to patient treatment (DE, MP), outcome assessments (RB, RH) and statistical analyses (SL, SR-H). Savitha Eranti (Clinical Research Worker), Andrew Mogg (Clinical Research Worker), Graham Pluck (Research Psychologist) and Richard Purvis (Research Psychologist) contributed to data acquisition, analysis and interpretation plus drafting of the manuscript. Martin Knapp (Professor of Health Economics) and Renée Romeo (Research Worker) undertook the economic analyses and Martin Knapp is the guarantor of the economic aspects of the report. John Rothwell (Professor of Neurophysiology) contributed to the original design with particular contribution to rTMS treatment.

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