Repetitive transcranial magnetic stimulation as a treatment for major depression

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MSAC Application 1101

Assessment report

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and costeffectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Dr Alun Cameron and Ms Brita Pekarsky from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S). The report was edited by ASERNIP-S.
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Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that uses rapidly changing magnetic pulses to investigate and modulate brain function. The magnetic field produced by the device is thought to cause depolarisation in certain areas of the cortex, although its exact mode of action is not fully understood. Over recent years rTMS has been used to treat a number of neuropsychiatric disorders including depression. There is still no consensus as to the best technique of rTMS to use for this purpose. The stimulation may be to the left or right dorsolateral prefrontal cortex, at low or high frequency (normally between 0.1 and 20Hz). There may also be variety in the intensity of the stimulation (normally at around 100% intensity) and the total number of pulses given each session. A course of treatment normally lasts between 1 and 4 weeks, with the patient receiving one session per weekday. The duration of each session is usually between 10 and 15 minutes.

The comparator for rTMS in this review is electroconvulsive therapy (ECT), as nominated by the applicant. The clinical decision pathway was constructed to account for this choice of comparator treatment. However, for the economic evaluation item drift was considered, that is, the effectiveness and cost-effectiveness of rTMS for patients who would not otherwise have been considered for ECT but may be referred for rTMS.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S) was engaged to conduct a systematic review of literature on repetitive transcranial magnetic stimulation as a treatment for major depression. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of repetitive transcranial magnetic stimulation as a treatment for major depression

Clinical need

Major depression is a chronic and debilitating disease accounting for 8 per cent of all years lived with a disability (YLD) in Australia, and 12 per cent YLD worldwide. The 12-month prevalence of depression in Australia is 4.2 per cent in adult males and 12 per

cent in adult females. Estimated costs to the health sector and loss of productivity, are considered to be in excess of $3 billion dollars annually. Major depression, or mood affective disorders, fall into two main types – unipolar disorder, and bipolar disorder.

At the moment, current treatment options for depression range from psychotherapy, pharmacotherapy and electroconvulsive therapy (ECT). Pharmacotherapy with anti-depressants is the primary treatment method. More modern medications have improved tolerability, although approximately one third of patients do not improve under recommended dosages of a range of anti-depressants within a period of approximately one month, and are classified as non-responders. Compliance with the medications is also acknowledged to be a problem.

ECT is a treatment option that is only conducted following the failure of other therapies. Patients must undergo a generalised seizure which necessitates the use of general anaesthesia and paralysing agents. ECT may be associated with short-term cognitive problems. Its mode of action is not completely understood, although it is considered by many to be the 'gold standard' treatment for anti-depressant resistant depression. Expert opinion of the Advisory Panel estimates that approximately 5 per cent of people with treatment resistant depression will take up this option each year.

Safety

There were seven comparative studies which compared rTMS with the comparator, ECT. Comparative safety outcomes were only reported in full, for both techniques, in a single study, and the result was inconclusive. ECT was associated with some short-term cognitive problems; however, all these problems recovered within one or two weeks after the end of treatment.

Absolute rTMS safety was determined by investigating all available studies (including case reports). Most adverse events reported (92%) were of low severity (such as headaches, mild pain and other transient problems). Seizures and psychosis were rare, and mania was seen mainly in patients suffering from bipolar depression. Therefore, overall, rTMS seemed to be a relatively safe procedure. However, there was no safety data for long-term or repeat use of rTMS. All the included studies investigated rTMS treatment for 3 to 4 weeks.

Effectiveness

Of the seven comparative studies, one study did not report baseline depression levels, and another was interested in cognitive effects and did not report depression outcomes in sufficient detail. These were not included in the meta-analyses in this review. Overall, there was a trend toward ECT being more effective than rTMS in the treatment of depression, although this effect was not statistically significant.

Where reported, all studies considered response to therapy to be a ≥50% reduction of the baseline value of a common depression scale. The mean of the response rate was 47.5 per cent for rTMS and 62 per cent for ECT. This difference was not statistically significant ($p=0.12$). There was evidence from a few studies that suggested that ECT and rTMS were equally effective in the treatment of non-psychotic patients. Due to the relatively small number of comparative studies available (7), and their reasonably similar

methodology, it was not possible to undertake any subgroup analyses (such as to investigate the effects of different rTMS treatments eg high or low frequency, or the effects of medications on treatment effectiveness).

For the purposes of the economic evaluation, the effectiveness of rTMS compared with sham rTMS (a placebo technique where the patient considers himself to be treated although no active therapy is given) was considered. This was considered important as many patients would refuse ECT and continue with ineffective anti-depressant medication, or have no treatment, in the absence of an alternative such as rTMS. Repetitive transcranial magnetic stimulation was more effective than sham treatment when outcomes were measured using the standard Hamilton depression rating scale and/or the number of responders. The number of responders to rTMS did not vary according to whether rTMS treatment was an add-on to medication, or was conducted on patients who had been washed-out from medication. However, the effectiveness of rTMS was reduced when we considered only patients who were stated to be medication-resistant. Studies which reported the highest response rates for rTMS over sham had the treatment over a longer duration than those which reported a poor response to rTMS.

In the course of completing the review, two new comparative studies were published which compared rTMS and ECT in the treatment of severe depression. These are discussed in the appendix as they were not identified as part of an updated systematic search strategy. Meta-analysis of these two studies in addition to the studies already included in the review showed that although overall the effect size of rTMS compared with ECT was similar, the new results showed ECT to be more effective than rTMS as a treatment for depression ($p=0.007$).

Cost effectiveness

The costs and consequences of rTMS vary in magnitude and direction by patient (who would otherwise have ECT and/or be hospitalised), site (multi-day or same-day admission, outpatient or private clinic) and sector (public or private). The added cost per additional responder (3 months depression-free) is estimated to be $1,952. It is expected that approximately 22,000 patients with severe to moderate treatment resistant depression (SMTRD) will have rTMS annually; of these 18,000 will not otherwise have had ECT, and of these, 9,000 will not have otherwise been hospitalised. The expected net increase in responders (5,756) and financial and resource implications (additional $12.9M to the MBS and $11.2M to health system overall) depends upon the mix of patients who have rTMS and uptake by SMTRD patients currently treated in the community. The expected freed same-day beds in public psychiatric hospitals or units (approximately 6,000) will be offset by the additional outpatient clinic sessions (approximately 14,000). There is a net increase in the total number of multi-day admissions (approximately 130) because only a small proportion of patients who would otherwise had ECT and a multi-day admission, are expected to have rTMS outside the hospital and hence free multi-day beds. Of patients who would otherwise have ECT and a multi-day admission, 59 per cent are expected to be non-responders to rTMS and 50 per cent of these are expected to have a follow-up admission for ECT (or a second admission if rTMS is as multi-day admission). It is unlikely that the entire estimated additional MBS rebateable private clinic consultations (80,000 or 5% of all current MBS rebateable consultations with psychiatrists) will be met within capacity. This will reduce the additional cost to the MBS but may be at a cost of displaced services.

Recommendation

MSAC recommended that on the strength of evidence pertaining to Application 1101, repetitive transcranial magnetic stimulation as a treatment for major depression, public funding should not be supported for this procedure.

- The Minister for Health and Ageing endorsed this recommendation on 4 June 2007 -

MSAC has considered the safety, effectiveness and cost-effectiveness of repetitive transcranial magnetic stimulation (rTMS) for moderate to severe refractory treatment resistant depression compared with electro convulsive therapy (ECT).

MSAC finds evidence that rTMS is safe and less invasive than ECT.

MSAC finds limited evidence that rTMS may be less effective than ECT.

The financial and resource implications will depend upon the mix of patients who have rTMS, including uptake amongst patients who would otherwise not have ECT.

At present, MSAC finds there is insufficient evidence to support public funding.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of Application 1101, repetitive transcranial magnetic stimulation, which is a therapeutic device for major depression. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for MSAC Application 1101, repetitive transcranial magnetic stimulation as a treatment for major depression.

Background

Transcranial magnetic stimulation (TMS) uses magnetic fields to bring about changes in electrical activity in localised areas of the brain cortex. This technique has been used over the past 20 years as a tool to investigate brain function and motor cortical activity in healthy individuals and in patients suffering from neurological conditions. Although its mode of action and effectiveness are not fully comprehended, it has been suggested that repetitive TMS (rTMS) may be used as a replacement for electroconvulsive therapy (ECT) in the treatment of medication-refractory major depression.

The procedure

Transcranial magnetic stimulation was introduced in the mid 1980s (Barker et al 1985). It is a non-invasive method of brain stimulation and has been used for examining conduction in central motor pathways, motor cortex excitability and other aspects of sensorimotor cortical physiology (Rothwell et al 1991; Manganotti et al 2001; Wassermann et al 2001; Shajahan et al 1999) including mapping cortical motor regions (Courturier 2005). Metal coils placed close to the head of the subject cause strong magnetic fields to bring about localised electrical changes in the brain cortex, which lead to neuronal depolarisation (Kozel & George 2002) and activation (Siebner et al 2000). Repetitive transcranial magnetic stimulation also may cause slight changes in regional cerebral blood flow (McNamara et al 2001; George et al 1999; Loo et al 2003; Zheng 2000), and may bring about small changes in the plasma levels of certain hormones (Evers et al 2001). The magnetic current can be delivered in a variety of manners. It may be as a single pulse (sTMS), or paired pulses that are a few milliseconds apart which are used to investigate the desensitisation of the neurones. Both of these techniques are often used in the study of motor functions. The pulses may also be delivered as a repetitive pulse (rTMS), when short magnetic pulses are delivered repeatedly in a train for many seconds or minutes (Burt et al 2002). Repetitive transcranial magnetic stimulation is the most frequently used technique for neuropsychiatric therapeutic purposes (Burt et al 2002) and is the subject of this report.

Repetitive transcranial magnetic stimulation has more recently been adopted in the treatment of numerous affective disorders, including depression. However, the physiological effects and efficacy of rTMS in this setting, and the ideal parameters of use are not fully understood and therefore the use of rTMS is still primarily that of a research tool.

There are many rTMS devices on the international market (manufacturers include Medtronic Inc. (USA), Magstim (UK), Cadwell Laboratories (USA), Neotonus Inc. (USA) and Neuronetics (USA)). Although most of these companies are based in USA, rTMS is not approved by the FDA for the treatment of depression. The device is comprised of a computer-controlled TMS machine whose capacitors deliver an electronic pulse to an insulated coil (copper or ferrous, round or figure-eight in shape), which produces a strong magnetic field. This magnetic pulse travels unimpeded through the skull (Kozel & George 2002) and is normally restricted to the underlying cortex (Ebmeier et al 2002). A Lycra cap is sometimes used to enable marking of the TMS coil position on the skull (Chistyakov et al 2005b).

In addition to the use of TMS in investigating motor cortical excitability, TMS has been used as a therapeutic tool in the treatment of many neuropsychiatric disorders, including depression (both bipolar and unipolar), mania (Grisaru et al 1998; Kapstan et al 2003), schizophrenia (Klein et al 1999b) and post-traumatic stress disorder (Cohen et al 2004). There has been a great deal of variability in the rTMS parameters used. As yet there is no real consensus on the specific parameters which are most effective for the treatment of depression, and no specific guidelines on its use in Australia (Ellis et al 2004). The main variable factor is the frequency of the magnetic stimulation. The number of pulses per minute can be described as low frequency (less than or equal to 1Hz) or high frequency (over 1Hz and typically no more than 20Hz) (Burt et al 2002). Repetitive transcranial magnetic stimulation can also be used at higher frequencies in order to deliberately induce seizures (Lisanby et al 2003; Kozel et al 2003), a technique known as magnetic seizure therapy. There is some evidence to suggest that low frequency can inhibit cortical stimulation, whilst high frequencies can activate certain areas (Martin et al 2003). When high frequency stimulation is used there is a requirement for a method of cooling the coil, which can become quite hot. This procedure can be done either by placing the coil on ice or through the use of a refrigeration device (Boechat-Barros et al 2004).

There is also slight variability in the intensity of the stimulation, as determined by the motor threshold used. This is the lowest intensity of stimulation that will cause consistent, standard muscle contraction in consecutive stimuli, often in the first dorsal interosseous or abductor pollicus brevis muscles (Burt et al 2002). The intensity of stimulation used for treatment is normally at, or near, this intensity (ie between 80–120% of motor threshold). The cortical region most often localised for stimulation during rTMS treatment is the left dorsolateral prefrontal cortex (left DLPFC) as it is thought to be the area which regulates mood (Padberg et al 2001) and is readily accessible to TMS (Courturier 2005), although other brain regions may be involved such as the parietal cortex and cerebellum (Schutter & van Honk 2005). The DLPFC is defined as '5cm anterior to the scalp position in the parasagittal plane for optimal stimulation of the abductor pollicis brevis muscle of the contralateral hand' (Padberg et al 1999; George et al 1995; Pascual-Leone et al 1996). Some studies record that high frequency left DLPFC, or low frequency right DLPFC, can be effective stimulation strategies in treating depression (Martin et al 2001). Concurrent electroencephalographic (EEG) and electromyographic (EMG) monitoring are common, especially at early stages of the treatment (Burt et al 2002).

The length of stimulation during rTMS treatment is normally a few seconds, although this may be longer if the frequency used is low. Following a short interval (of up to one minute), the stimulation is repeated. This repetition is known as a train, which may be up to 20 stimulations in total and take from a few minutes to 60 minutes to perform (Burt et al 2002), although this is most frequently about 10 to 15 minutes. During treatment the patient is fully awake and seated comfortably with both forearms supported. The patient is usually required to take a course of this treatment, which normally comprises one session on consecutive working days for between one and four weeks.

There are some known side-effects of rTMS treatment. Most are mild and range from headaches (which can usually be treated using a mild analgesic such as aspirin), scalp pain at the site of stimulation, or ear pain as a result of the noise of the pulses from the coil (which may be avoided through the use of ear plugs). The most serious side-effect is the risk of seizure (Wassermann 2000; Rosa et al 2004). This is a severe hazard, but is quite rare, and can be avoided with the use of current safety parameters (Rosa et al 2004; Wassermann 1998). At this stage, any long-term side-effects of rTMS treatment,

especially when used as a maintenance treatment, are unknown (Wassermann 2000). There is some evidence that low frequency stimulation may pose a lower risk of seizure than high frequency stimulation (Wassermann 1998).

As a consequence of this risk, guidelines recommend that rTMS is contra-indicated in patients who have a personal or first-degree family history of seizure (Wassermann 1998). Other contra-indications for the use of rTMS are similar to those applied to the use of electroconvulsive therapy (ECT), many for historical reasons. These include pregnancy, ferromagnetic metallic implants, neurological abnormalities and head injury. Unlike ECT, rTMS avoids the side-effects associated with anaesthesia and muscle relaxation as these are not required, and is also associated with fewer cognitive side-effects (Kozel & George 2002). Repetitive transcranial magnetic stimulation generates comparable current densities in the brain to ECT, although this is localised (Sekino & Ueno 2002). A study based in Tasmania suggests that the majority of patients who had received rTMS considered it to be a more acceptable treatment that ECT (Walter et al 2001). Therefore it is possible that rTMS may enhance patient options in the treatment of medication-resistant depression (Fitzgerald 2004).

A number of reviews and meta-analyses of rTMS as a treatment for depression have been published over the past few years. Overall, most show a positive result for high frequency left DLPFC Repetitive transcranial magnetic stimulation over sham treatment (McNamara et al 2001; Holtzheimer et al 2001; Burt et al 2002; Kozel & George 2002; Martin et al 2001; Loo et al 2005), where the TMS coil is pointed away from the skull so as to act as a placebo (Loo et al 2000). Three meta-analyses concluded there was insufficient evidence to show that rTMS was more effective than sham (Aare et al 2003; Couturier 2005; Martin et al 2003).

Currently in Australia, rTMS is not commonly used in the treatment of depression (Ellis et al 2004), and its suggested use is limited to hospital-based units, with access to ventilation equipment and resuscitation equipment, within a research protocol (see The Royal Australian and New Zealand College of Psychiatrists Position Statement #40, http://www.ranzcp.org/publicarea/posstate.asp).

Depression

Depression is a significant public health problem worldwide (AIHW 2002). The Australian Bureau of Statistics defines depression as 'a state of gloom, despondency or sadness lasting at least 2 weeks'. Periods of depression may occur as discrete events or as recurrent over the lifespan. Episodes of major or clinical depression may be further divided into mild, major or severe (Asberg et al 2004). Results from the National Comorbidity Survey Replication (NCS-R) undertaken in the United States indicated that over half of the total cases of depression were diagnosed as being either severe or very severe (Kessler et al 2003). Depressive disorders are long-term conditions which vary in their severity, with periods of symptoms (constituting a depressive episode) and periods of remission (Ellis et al 2004).

The Diagnostic and Statistical Manual of Mental Disorders, version four (DSM-IV), published by the American Psychiatric Association, is the diagnostic system most commonly used to diagnose mental disorders. The current International Statistical Classification of Diseases and Related Health Problems (ICD-10), as published by the

World Health Organisation, is a frequently used international alternative (www.who.int/classifications/isd/en).

According to the DSM-IV scale, a mental problem is classified as depression, or major depressive disorder, when at least 5 of the 9 symptoms below are present (Ellis et al 2004):

- depressed mood most of the day
- loss of activity or pleasure (in all or most activities, most of the day)
- large increases or decrease in appetite (large weight gain or loss)
- insomnia or excessive sleeping (hypersomnia)
- restlessness as evident by hand wringing and similar other activities (psychomotor agitation) or slowness of movement (psychomotor retardation)
- fatigue or loss of energy
- feelings of worthlessness, or excessive inappropriate guilt
- diminished ability to concentrate, or indecisiveness
- recurrent thoughts of suicide or death.

Major depression, or mood affective disorders, fall into two main types. These are unipolar disorder (including major depressive disorder) (Ellis et al 2004) and bipolar disorder (Mitchell et al 2004). Uni-polar disorder is characterised by depression without periods of elation or mania. Bi-polar depression is characterised by periods of mania or hypomania, depression and 'mixed episodes' or 'dysphoric mania' (both manic and depressive symptoms) (Mitchell et al 2004). The DSM-IV and the ICD-10 have both divided bipolar disorder into two types, bipolar I (at least one manic episode) and bipolar II (hypomania and depression). Both are severe and debilitating conditions.

The DSM-IV describes an episode of mania as 'a distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least one week' (or requiring hospitalisation). In addition, the DSM-IV requires at least four of the following seven symptoms (three if merely irritable):

- inflated self-esteem or grandiosity
- decreased need for sleep
- more talkative than usual
- flight of ideas, racing thoughts
- distractibility
- increase in goal-setting activity or psychomotor agitation
- excessive involvement in pleasurable activities (such as buying sprees, sexual indiscretions, or foolish business investments).

These symptoms must be severe enough to interfere with work or social relations or necessitate hospitalisation to prevent harm to oneself or others.

Existing procedures

Psychotherapy

Psychotherapy covers a range of techniques to improve people's mental health and behaviour, usually through discussions between therapists and their clients. Although the focus of different therapies vary, they all deal with behaviour patterns, cognitive dysfunctions and relationship issues that are linked to a person's depression (Asberg et al 2004). Psychotherapy may be a first-line treatment for patients who are reluctant to start pharmacotherapy, or patients who have comorbid medical conditions and are unable to tolerate anti-depressants (Mahendran & Yap 2005). A range of psychological treatments may benefit patients, but the style, intensity and focus will vary among individuals (Mitchell et al 2004). In general, the response to psychotherapy takes longer than the response to a single medication (Arnow & Constantino 2003).

Psychotherapy treatment may be conducted individually or in groups. Group therapy has been found to be beneficial when used as an adjunct to medication in the treatment of various phases of bipolar illness (Joffe 2002).

The most basic form of psychotherapy is psycho-education, which provides the patient with information about their illness and the treatments, including side effects (Joffe 2002). This therapy deals with the long-term course of the illness and recurrent and future depressions, rather than managing acute depressive episodes (Joffe 2002).

Cognitive therapy uses short structured sessions aimed at modifying a person's distorted thinking to change their core beliefs and relieve symptoms (Rupke et al 2006). The fundamental assumption of cognitive therapy is that a thought precedes a mood; therefore, learning to substitute healthy thoughts for negative thoughts will improve a person's mood, self concept, behaviour and physical state (Rupke et al 2006). Behavioral counselling interventions assist patients in adopting, changing, or maintaining behaviors proven to affect health outcomes and health status. Behavioural counselling uses techniques such as role playing, modelling and other conditioning techniques which are used to bring about measurable and observable changes. Cognitive behavioural therapy (CBT) is a combination of the cognitive therapy and behavioural counselling approaches (Parker et al 2003). CBT is very goal oriented and is considered a very effective therapy. It requires active participation by the client and involves more activity scheduling and behavioural conditioning than classic cognitive therapy (Rupke et al 2006). Interpersonal and social rhythm therapy (IPSRT) combines interpersonal psychotherapy (Klerman et al 1984; Weissman et al 2000) for the treatment of unipolar depression, together with a circadian rhythm model (Ehlers et al 1988; Swartz et al 2004). Patients learn how to regulate routines in day-to-day life, such as setting daily times for sleep, eating and exercise, and to address personal problems linked to the onset and persistence of their disorder (Mitchell et al 2004).

It has been suggested that counseling and supportive therapy alone will often benefit patients with mild symptoms but that it is insufficient for severe and/or psychotic major depressive disorder (Mahendran and Yap 2005). The Australia and New Zealand clinical practice guidelines for bipolar disorder recommend that psychotherapy is most effective when used in conjunction with pharmacotherapy and is best begun when the person is relatively well (Joffe 2002; Mitchell et al 2004). In chronic major depression, combined

treatment has demonstrated significant outcome superiority over medication or psychotherapy alone (Arnow & Constantino 2003).

Pharmacotherapy

Pharmacotherapy is one of the two primary methods for the treatment of depression, the other being psychotherapy. As with other methods of treatment, the effectiveness of pharmacotherapy depends on more than just the medication itself. Factors such as the length of time the patient has been depressed, the severity of symptoms, results of previous treatments, support from family and friends and the person's willingness and ability to undergo treatment will significantly influence the degree of effectiveness of the treatment.

Prescription of medications for the treatment of depression is common and as a result there is a wide variety of drugs available. A list of the classes of medications used to treat depression along with examples of drugs available in Australia is provided in Table 1.

These drugs are classified into different classes according to the neurotransmitters or receptors which they affect (Table 1). Drugs which act on one neurotransmitter are called selective anti-depressants while those which act on two or more are termed broad spectrum anti-depressants. Broad spectrum anti-depressants (eg TCAs) are generally very effective because they act on a wider range of neurotransmitters and receptors but at the same time they are associated with more adverse events than selective anti-depressants (eg SSRIs) due to their wider range of action.

Table 1 Classes of drugs for the treatment of depression

Name		Examples
Monoamine Oxidase Inhibitors	MAOI	Phenelzine (Nardil), tranylcypromine (Parnate)
Tricyclic Anti-depressants	TCA	Nortriptyline (Allegron), clomipramine (Anafranil), dothiepin (Prothiaden, Dothep), imipramine (Tofranil) and amitriptyline (Tryptanol, Endep)
Selective Serotonin Reuptake Inhibitors	SSRI	Setraline (Zoloft), citalopram (Cipramil, Ciazil, Talohexal), paroxetine (Aropax, Paxtine), fluoxetine (Prozac, Erocap, Lovan, Zactin, Auscap), fluvoxamine (Luvox, Faverin).
Noradrenaline Reuptake Inhibitors	NARI	Reboxetine (Endronax)
Serotonin and Noradrenaline Reuptake Inhibitors	SNRI	Venlafaxine (Efexor, Efexor-XR)
Reversible Inhibitors of Monoamine Oxidase – A	RIMA	Moclobemide (Aurorix, Arima)
Noradrenaline Serotonin Specific Anti-depressants	NaSSA	Mirtazapine

It is widely acknowledged that in general the majority of anti-depressants confer similar levels of efficacy in the treatment of depression (Ellis et al 2004; Geddes 1999). In addition, this similarity has been observed in both patients suffering unipolar and bipolar depression (Gijsman et al 2004).

Table 2 Common side effects of medications used for the treatment of depression

Class	Common side effects
SSRI	Nausea, agitation, sleep disturbance, sexual dysfunction, headaches
SNRI	Nausea, anxiety, fatigue, sexual dysfunction, headaches
RIMA	Headaches, dizziness, nausea or heartburn, increased sweating
TCA	Sedation, sleepiness, dry mouth, constipation, low blood pressure, falls
NaSSA	Sedation, dizziness, increased appetite and weight gain
NARI	Dry mouth, constipation, agitation, dizziness, headache, sexual difficulties, difficulty urinating, increased heart rate, increased sweating
MAOI	Drowsiness, lethargy, insomnia, headache, dizziness, nausea or heartburn, dry mouth, blurred vision, constipation, increased sweating, muscle tremor, loss of appetite

MAOI, Monoamine Oxidase Inhibitors; TCA, Tricyclic Anti-depressants; SSRI, Selective Serotonin Reuptake Inhibitors; NARI, Noradrenaline Reuptake Inhibitors; SNRI, Serotonin and Noradrenaline Reuptake Inhibitors; RIMA, Reversible Inhibitors of Monoamine Oxidase – A; NaSSA, Noradrenaline Serotonin Specific Anti-depressants

Pharmacological treatment, however, is often associated with the presence of unfavorable side effects for the patient (Table 2) (Jordan 2005). In addition, patients being taken off medication may experience withdrawal symptoms, especially following an abrupt discontinuation of the medication (Haddad 2001; Antai-Otong 2003; Maixner & Greden 1998). Furthermore it has been acknowledged that compliance with prescribed medication is poor in patients suffering from depression (Stimpson et al 1999). Given these factors, pharmacological therapy presents challenges to both patient and doctor.

For the above reasons patients suffering from depression require close supervision throughout pharmacological treatment. Should medication not be taken as directed, relief of symptoms may not occur (Maixner & Greden 1998). Maintaining compliance is therefore important but may be difficult considering that the time of action for many anti-depressants is approximately two weeks, and that the time required to evaluate the efficacy of a drug in a patient may be an additional four weeks (Barbui et al 2000). In such situations some patients may feel that the medication is not working and may be tempted to discontinue treatment (Barbui et al 2000). This problem is further magnified by the fact that at times the side effects of the medication may appear before any anti-depressant effect has taken place, giving a false sense that the medication has failed. On the other hand, patients who quickly feel better after taking medication may be tempted to discontinue medication early. In both situations it is important to maintain taking the medication for the duration of time as advised by the doctor as non-compliance can potentially lead to future relapses. Upon successful treatment of an initial depressive episode it is recommended that treatment continues for a period of 6 to 12 months (Barbui et al 2000). For recurrent episodes treatment duration may be as long as 3 to 5 years (Barbui et al 2000). For patients suffering from bipolar disorder, pharmacological therapy may continue indefinitely[1].

When first prescribing medications, a doctor may need to prescribe a variety of different anti-depressants before finding the most effective one for the patient[1]. Therefore in the search for the most effective medication, a patient may grow increasingly discouraged and frustrated, perhaps leading to pessimism and potential non-compliance in the future.

[1] Retreived January 2007 from http://www.nimh.nih.gov/publicat/depression.cfm

Patients who do not respond to one type of anti-depressant are often given an alternative from a different chemical class (Remick 2002). Despite their effectiveness in treating depression, approximately one third of patients receiving anti-depressants do not improve under recommended dosages and are classified as non-responders (Stimson et al 1999). There is sparse data for the proportion of patients who are resistant to two or more trials of anti-depressant medication; however, the recent large STAR*D study suggested that this would approximate to around 15 per cent (Fava et al 2006).

Some patients may experience a partial improvement in symptoms between 3 and 6 weeks after treatment commenced. In order to achieve full resolution, the medication dosage may be increased or augmentation may be required. Typically small doses of either lithium, liothyronine sodium or a psycho-stimulant are able to induce a complete response within 1 to 2 weeks in a quarter of patients (Remick 2002). Lithium is a popular choice in patients with both unipolar and bipolar depression; however, it carries the potential for cognitive side effects as well as weight gain among others (Freeman & Freeman 2006).

Tranquilisers and sedatives can be sometimes given to a patient in order to calm anxiety and to promote sleep. Patients who suffer from psychotic depression may also receive antipsychotic medication which is also often associated with unfavourable side effects including extra-pyramidal effects, hyperprolactinaemia, seizures, hypotension, anticholinergic effects and weight gain (Wijkstra et al 2005).

In cases where there is a similarity in the level of effectiveness in various types of drugs, the choice of drug is influenced by its potential side effects, toxicity and cost. Because each patient has different levels of tolerability, patients would require custom designed drug regimens in order to minimise any negative effects of drugs.

In Australia, the first choice and most commonly prescribed anti-depressants are the SSRIs as they are seen to be the most safe and also highly effective[2]. However, despite SSRIs being effective and safe, the use of this family of drugs is often associated with a variety of side effects, as are all the other classes of anti-depressants.

Electroconvulsive therapy

Electroconvulsive therapy (ECT) was first introduced as a treatment for mental disorders in 1938 by Cerletti and Bini (Endler 1988). It continues to be widely used in psychiatric practice as a treatment for selected neuropsychiatric illnesses, such as depression, schizophrenia, catatonia and mania, despite being a sometimes controversial shock therapy involving the induction of a generalised seizure in the patient by passing a large electric current through the brain. Views on ECT range from the belief that it is safe and effective (Fink 2000), to those that consider it to be a dangerous and ineffective procedure (Sterling 2000).

Despite over 50 years of research into ECT, there is still no agreement on the mechanisms of action of the treatment (Fink 2001; Greenhalgh et al 2005). Additionally, there is little consensus regarding the mental disorders for which ECT is indicated, its

[2] Retreived January 2007 from http://www.beyondblue.org.au

efficacy in treatment, the optimal methods of administration, possible complications, and the extent of its usage in various settings, or the ethics of the procedure (Reisner 2003).

ECT treatment generally requires the services of a qualified psychiatrist, an anaesthetist, a registered nurse and a clinical nurse (Vic Dept Human Services 2000). The patient is placed under general anaesthetic and ventilated with 100% oxygen. Electrodes are placed on the patient's head, either bilaterally or unilaterally on the dominant or non-dominant side of the brain. An electric current is then passed through the patient's brain to induce a controlled convulsion that lasts approximately 35 seconds by electroencephalogram (EEG). A large current is required to cause a seizure as the skull and surrounding tissue are inherently insulating to electricity (Sekino & Ueno 2002). Prior to administering the electric current, a paralysing agent is given to the patient to suppress the peripheral manifestations of the seizure, protecting the patient from fractures caused by muscular contractions and other orthopaedic complications and injuries induced by the seizure. Systemic changes that may occur during ECT include a brief episode of hypotension and bradycardia, followed by sinus tachycardia and sympathetic hyperactivity with an increase in blood pressure (Kelly & Zisselman 2000). These changes are transient and typically resolve over the course of minutes.

The entire procedure, from beginning to end, lasts about 30 minutes. In most cases, the total number of treatments a patient will receive depends upon many factors such as age, diagnosis, the history of illness, family support and response to therapy (Vic Dept Human Services 2000), but in most cases ECT is administered in a series of treatments two to three times per week until resolution or maximal improvement of target symptoms, such as sleep, appetite, energy and activity levels (Kelly and Zisselman 2000). Patients typically receive 6 – 12 treatments, at a frequency of about 3 per week, per course of ECT (Datto 2000).

Modern ECT devices deliver a constant current brief pulse stimulus, allow the performance of both bilateral and unilateral non-dominant hemisphere stimulation, and enable individualised adjustment of stimulus intensity parameters (Kelly and Zisselman 2000). These devices result in less cognitive side effects than the sine wave machines used previously (Donnelly et al 2006). The optimal method for selecting a stimulus dose in ECT continues to be an area of controversy (Kelly & Zisselman 2000; Donnelly et al 2006). The efficacy of the ECT can be affected by the degree to which the electrical dose lies above seizure threshold. The seizure threshold is defined as the minimum charge necessary to produce a generalised motor seizure, and can vary greatly among patients (Greenhalgh et al 2005). It has been demonstrated that the efficacy and cognitive effects of ECT increase as the ECT stimulus exceeds the individual patient's seizure threshold (Kelly & Zisselman 2000). Whereas bilateral ECT requires a stimulus just above seizure threshold, unilateral electrode placement requires a stimulus dose of at least 2.5 times seizure threshold (Beale 1998).

In most circumstances, ECT is conducted after other modes of treatment, such as pharmacotherapy and cognitive therapy have failed. The American Psychiatric Association (APA) guidelines recommend that ECT should primarily be used: where there is a need for a rapid response ie if a patient is suicidal, self-injurious, refuses to eat or drink, cannot or will not take medication as prescribed, or presents some other danger to themselves; where the risks of other treatments outweigh the risks of ECT; where there is a history of poor medication response or a good response to ECT; or where the patient requests it (APA 2001). The Australian and New Zealand guidelines suggest that a specialist should rely on experience rather than the limited literature on whether or not

to use ECT as a therapy and to start with unilateral treatment unless the patient's prior treatment or urgency dictate otherwise (Ellis et al 2004).

Even though the incidence of adverse events has decreased over the years as ECT technique has improved, side effects are not uncommon (APA 1990). Efficacy of ECT is influenced by the positioning of electrodes and dosage of electricity (UK ECT Review Group 2003). It has been found that gains in the efficacy of ECT in the treatment of depression are achieved at the expense of an increased risk of cognitive side effects (Greenhalgh et al 2005; UK ECT Review Group 2003).

Cognitive impairments associated with ECT treatment mostly reflect changes in memory, such as temporary anterograde amnesia and retrograde amnesia (UK ECT Review Group 2003). Following ECT treatment, the patient may also experience some confusion, headache, nausea and myalgia (reviewed by Datto 2000). These side effects generally clear over the course of several weeks following completion of the treatment series but memory problems can take longer to resolve (Reisner 2003). There is no evidence that ECT results in the loss of memories formed prior to the time of treatment or that it affects the patient's future ability to learn (Asberg et al 2004). There is also no evidence that ECT causes structural brain disease (Devanand et al 1994, Abrams 2000).

According to the Australian and New Zealand clinical guidelines for the treatment of depression, raised intracranial pressure is the only absolute contraindication for ECT, but situations of risk requiring careful evaluation include hypertension, recent myocardial infarction, bradyarrhythmias, cardiac pacemakers, intracranial pathology, aneurysms, epilepsy, osteoporosis, skull defect, retinal detachment and concurrent medical illnesses (Ellis et al 2004). Overall, ECT has been reported to carry a very low risk of death, with approximately two to four deaths per 100,000 treatments, which is comparable to the number of deaths from general anaesthesia inductions alone (Abrams 1997). Other authors believe the risk to be higher due to overlooked respiratory complications (Tecoult & Nathan 2001).

ECT is still considered to be the most effective treatment for major depression (Grunhaus et al 2002). Contrasting reports exist regarding its efficacy in different clinical situations, and include, but are not limited to, the severity of depression and the response to ECT (Kindler et al 1991; Sackheim et al1987), the duration of the current depressive episode and response to ECT (Kindler et al 1991; Prudic et al 1996), and the effectiveness of ECT in patients who do not respond to pharmacotherapy (Tsuchiyama et al 2005; Prudic et al 1990; van den Broek et al 2004; Pluijms et al 2002). There is little evidence regarding the long-term efficacy of ECT (Greenhalgh et al 2005; UK ECT Review Group 2003). ECT is an effective short-term treatment for patients with depressive illness and it is probably more effective than drug therapy (UK ECT Group 2003). The Australian and New Zealand Guidelines acknowledge that the benefits of ECT are short term and recommend that it should be followed with maintenance medication (Ellis et al 2004).

Comparator

The comparator for this review is electroconvulsive therapy.

Use of electroconvulsive therapy in Australia

According to the Medicare Benefits Schedule, there were 18,077 services for 1,861 patients offered for electroconvulsive therapy, with or without the use for stimulus dosing techniques, including any electroencephalographic monitoring and associated conditions (item number 14224), in the financial year 2005-06. For Medicare item number 20104 (anaesthetic for ECT procedures) there were 19,076 services for 1,887 patients in the same financial year.

In the public sector, according to the Australian Refined Diagnosis Related Group (AR-DRG), there were 13,912 services offered for ECT as a same-day mental health treatment (item number U40Z) in the financial year 2004-05. The AR-DRG code does not signify whether this was done as an inpatient or as an outpatient service. There were no other listings for ECT, for example for multi-day treatments with ECT, and no information was available regarding patient numbers treated. The number of ECT services offered through the DRG has increased steadily since 1997 when less than half the current number of services (5,431) was offered.

Expert opinion from the Advisory Panel suggests that the number of ECT sessions per course of treatment would be between 6 and 10. Data from Medicare records, as listed above, suggests that each patient receives on average 10 ECT treatments per year. Using the above figures, the numbers of patients receiving ECT in the public sector would approximate to 1,391 (in 2004-05). Consequently the total number of patients treated with ECT in the public and private sectors would be approximately 3,252. Assuming that this represents only approximately 5 per cent of all patients who are resistant to medication (an estimate from the expert opinion of the Advisory Panel), the total number of patients in Australia who could be considered for ECT (and therefore potentially for rTMS) may be about 65,000.

Choosing between repetitive transcranial magnetic stimulation and electroconvulsive therapy

The decision about whether to treat a patient with rTMS or ECT is complex and takes into account the following:

- Patient choice. A patient may be more willing to accept rTMS as a treatment, rather than ECT (Walter et al 2001).

- Access to treatment. ECT is often restricted to use in hospitals, due to the requirement of general anaesthesia for day-patients or prolonged admissions. Repetitive transcranial magnetic stimulation may be available in clinics and outpatients departments so may be more easily accessible. The current Royal Australian and New Zealand College of Psychiatrists (RANZCP) position statement on rTMS recommends that the procedure be carried out in a hospital setting, and that resuscitation equipment should be available in the event of a seizure.

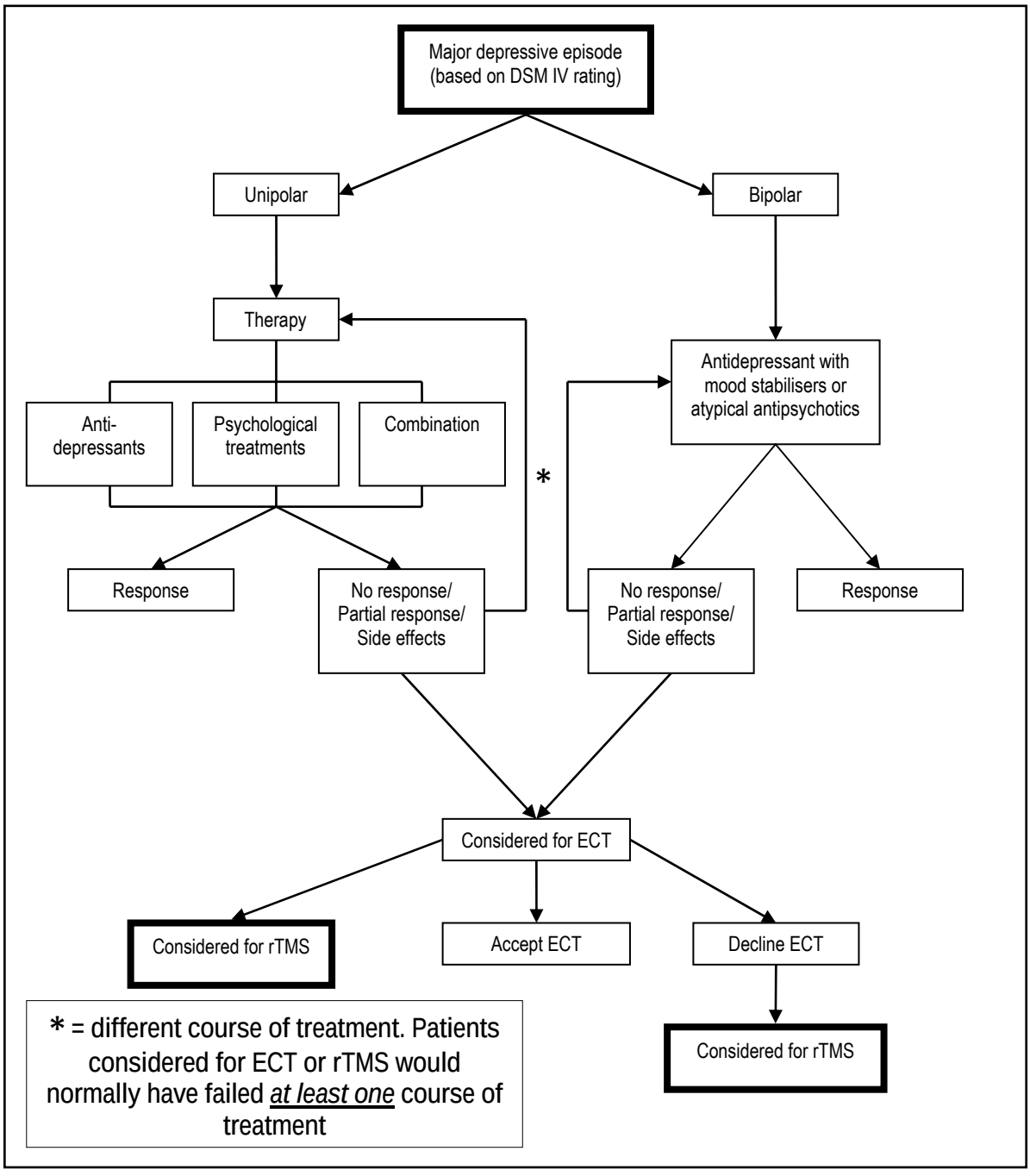
- Compliance. Repetitive transcranial magnetic stimulation requires more frequent treatments than ECT; therefore, patient compliance is an important issue to consider.

- Safety protocols and contraindications. At the moment, current safety protocols and contraindications for both rTMS and ECT are similar.

- Other factors. These include psychosis, patient age, severity of depression and pregnancy.

Clinical decision pathway

Figure 1 Clinical decision pathway for the treatment of a major depressive episode, as determined by the DSM-IV classification



Clinical need / burden of disease

Major depressive disorder is a common illness, causing a great deal of morbidity in Australia and throughout the world. Worldwide, according to the World Health Organisation, in the year 2000 depression was the fourth leading cause of burden among all diseases, accounting for 4.4 per cent of total disability-adjusted life-years (DALYs) (Ustun et al 2004). However, it was the leading cause of non-fatal burden, accounting for almost 12% of all total years lived with disability (YLD). Table 3 summarises the worldwide incidence and prevalence for depression.

Table 3 Worldwide incidence and prevalence of major depressive disorder (Ustun et al 2004)

	Worldwide cases of depression, per 100,000 per year	
	Male	Female
Incidence	3199	4930
Prevalence	1607	2552

In Australia, depression is the most debilitating illness, accounting for 8 per cent of all years lived with disability (Hickie 2004; Mathers et al 1999). In comparison, ischaemic heart disease contributes about 3 per cent, and drug dependence or abuse about 2 per cent of disease burden (Mathers et al 1999). A study conducted by the Australian Bureau of Statistics found that 17.7 per cent of a sample of 10,600 people had one or more common mental disorders. There was a 12-month prevalence of depression (as characterised by an ICD-10 diagnosis) of 4.2 per cent in males, and 12 per cent prevalence in females (Henderson et al 2000). Importantly, this study showed that fewer than half of depressed people had sought help from health services in the previous 12 months. The estimated costs (direct and indirect) of depression in Australia are substantial, thought to be in excess of $3 billion dollars annually (Hickie 2004; Mathers et al 1999).

In comparison, a large survey was undertaken during 2001 and 2002 in the USA, as an expansion of the above WHO survey (Ustun et al 2004). This indicated a lifetime prevalence of major depressive disorder (using the DSM-VI system and a fully structured diagnostic interview) was 16.2 per cent, and 12-month prevalence 6.7 per cent (Kessler et al 2003; Kessler et al 2005; Kessler et al 2005). Interestingly, a large proportion (50.2% of all cases) were recorded as being severe or very severe (Kessler et al 2003). As with the Australian study, a relatively small proportion (37.4%) sought treatment during the first year of onset (Wang et al 2005).

Marketing status of the device / technology

According to the applicant it is being used for a limited number of patients in Tasmania and Victoria within Australia. The technology has been approved for use in some countries (for example Canada and Israel) and is awaiting FDA approval in USA.

The device being applied for use with the procedure is the Dantec MAGPRO magnetic stimulator; product ID 173313, by sponsor Medtronic Australasia Pty Ltd (Table 4). This device is not exempt from the regulatory requirements of the Therapeutic Goods Act 1989. It has been registered with the TGA on the Australian Register of Therapeutic

Goods under listing/registration number 99827 with the indication Magnetic Stimulation.

Table 4 Devices listed on the on the Australian Register of Therapeutic Goods

Product number	Description	Sponsor	ARTG number
173313	MAGPRO – Stimulator, magnetic	Medtronic Australasia Pty Ltd	99827
68387	The Magstim 200	Medtel Pty Ltd	23492
135717	The Magstim magnetic induction coils (various)	Medtel Pty Ltd	23492
135719	Magstim magnetic stimulators 220, 250, 500	Medtel Pty Ltd	23492
135720	Magstim with booster modules (various)	Medtel Pty Ltd	23492

Current reimbursement arrangement

There is currently no item number for rTMS in the Medical Benefits Schedule.

Approach to assessment

Search strategy

The medical literature was searched to identify relevant studies for the period between 1990 and 2006. Repetitive transcranial magnetic stimulation was developed in the early- to mid-1990s. Searches were conducted via MEDLINE (1966-2006), EMBASE (1980-2006), Current Contents, PubMed, PsycINFO (1985-2006) and the Cochrane Library. International Network of Agencies for Health Technologies (INAHTA), International Society for Technology Assessment in Health Care (ISTAHC), The York Centre for Reviews and Dissemination databases (UK), Clinicaltrials.gov, NHS Health Technology Assessment (UK), National Research Register (UK), relevant online journals and the internet were also searched. Searches were conducted without language restriction.

Searches were designed to be as broad as possible. Search terms for Embase (1980 – 8 May 2006), Medline (1966 – 8 May 2006) and PsycINFO (1985 – 8 May 2006) were as follows:

1. Transcranial magnetic stimulation.mp (keyword search) or exp *Transcranial magnetic stimulation/
2. tms.mp (keyword search)
3. Magnetic seizure therapy.mp (keyword search) or exp *Magnetic seizure therapy
4. exp. *Depression/
5. depress$.mp (keyword search)
6. exp *Bipolar/
7. bipolar.mp (keyword search)
8. (1 or 2 or 3) and (4 or 5 or 6 or 7)

Search terms for Current Contents (1998 – 2006) were as follows:

1. TS=(TMS)
2. TI=(TMS) OR TI=transcranial magnetic stimulation
3. TS=transcranial magnetic stimulation
4. TS=magnetic seizure therapy
5. TS=depress*
6. TS=bipolar
7. #1 or #2 or #3 or #4
8. #5 or #6
9. #8 and #7

Search terms for the Cochrane Library were: transcranial magnetic stimulation; TMS; magnetic seizure therapy.

Inclusion criteria

Table 5 Inclusion/exclusion criteria for identification of relevant studies for rTMS as a treatment for depression

	Inclusion criteria	Exclusion criteria
Participants	Human studies of adult patients where the treatment of major depressive episode is the primary concern (include treatment of people with unipolar and bipolar disease)	Experimentation with healthy volunteers Experimentation with animals Depression as a result of a co-morbidity (eg secondary to stroke, Parkinson's disease etc.) Treatment of schizophrenia
New intervention	Repetitive transcranial magnetic stimulation (rTMS). Treatment combined with any procedure (including psychotherapy or psychotropic drugs)	
Comparative intervention	Electroconvulsive therapy (ECT)	
Outcomes	Peri- and post-treatment morbidity and mortality Effectiveness and durability of treatment, including but not limited to: technical success remission Patient-relevant outcomes, including but not limited to: survival psychological and psychosocial outcomes (measured with accepted scales eg the Hamilton Depression Rating Scale, Montgomery-Asberg Scale) cognitive outcomes functional and neurological outcomes suicide rates quality of life return to work / normal activities Complications, including but not limited to: technical clinical (transient or permanent neuropsychological deficits) seizures impaired hearing transient scalp pain Cost and resource use issues	Technical not clinical outcomes
Types of studies	Randomised comparative studies will be included for safety and effectiveness. Non-randomised comparative studies, case series and case reports will be included for safety only. Safety outcomes included will be seizures, neuropsychological impairment, cognitive impairment, headaches, scalp pain, auditory problems, suicide and death	
Language	Studies in languages other than English will be included if they add substantially to the English language database	

Review of literature

Literature databases

Articles were retrieved if they were judged to possibly meet the inclusion criteria. Two reviewers independently applied the inclusion criteria and any differences were resolved by discussion. Excluded studies are listed in Appendix D with reasons for exclusion. The bibliographies of all retrieved publications were handsearched for any relevant references missed in the database search (pearling).

Data extraction

Data was extracted by one researcher and checked by a second using standardised data extraction tables developed a priori. Data was only reported if stated in the text, tables, graphs or figures of the article, or if they could be accurately extrapolated from the data presented. If no data were reported for a particular outcome then no value was tabulated.

Description and methodological quality of included studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC, 2000).

These dimensions (Table 6) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of its determination.

Table 6 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

NOTE *See Table 7

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 7.

Table 7 Designations of levels of evidence*

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

NOTE *Modified from NHMRC, 1999.

Included studies were critically appraised for study quality according to the guidelines in Chapter 6 of the Cochrane Reviewers' Handbook (Higgins & Green 2005). Included randomised controlled trials (RCTs) were examined with respect to the adequacy of allocation concealment and blinding (if possible), handling of losses to follow-up, and any other aspect of the study design or execution that may have introduced bias. Two reviewers critically appraised each of the included studies, and any differences in interpretation were resolved through discussion. A quality score was not assigned, instead the quality of the included studies was described in a narrative fashion, and any important quality issues were highlighted in the discussion of outcomes.

Data analysis

Meta-analysis

Where outcomes of RCTs could be sensibly combined (outcomes measured in comparable ways and no apparent heterogeneity), relative risks or weighted mean differences with 95 per cent confidence intervals (CI) were calculated using RevMan 4.2 (Update Software). Relative risks or weighted mean differences were also calculated for some outcomes of individual RCTs as an aid in the interpretation of results. The confidence intervals represent a range within which the 'true' value of an effect size is expected to lie, with a given degree of certainty eg 95 per cent CI.

Subgroup analyses were carried out for certain variables where possible.

Handling of non-randomised data

Where statistical pooling was not possible, medians of rates (for dichotomous outcomes) or medians of means (for continuous outcomes) for all studies reporting the outcome were calculated. The data was presented according to the comparison (eg rTMS alone vs ECT alone) or rTMS alone (for case series and case reports).

The following subgroups were also examined narratively:

- Patients with psychosis.
- Patients with significant comorbidities.

Included and excluded studies

The studies identified as fulfilling the inclusion criteria for the review are listed in Appendix C. The studies which were excluded from the review are listed in Appendix D, together with the reason for exclusion.

Current trials

Websites of clinical trials agencies were searched to identify all relevant ongoing or unpublished clinical trials. These included the Australian Clinical Trials Registry, ClinicalTrials.gov, the National Research Register (UK) and Controlled-Trials.com. As of 15 June 2006 there were 22 ongoing trials for rTMS, mostly comparing rTMS with sham treatment. About half of the trials had been completed. Of particular interest were the following three trials:

McLoughlin D (contact person), Institute of Psychiatry, London, UK

'Clinical effectiveness of rTMS versus ECT in severe depression: a multi-centre randomised controlled trial and economic analysis'. Completed April 2005. The manuscript is currently under peer review, with an expected publication date of late 2006. This study includes approximately 180 patients with a 6 month follow-up, and was single-blinded. Most patients were in-patients during the treatment phase and remained on their usual medication after treatment allocation. See the National Research Register for more information, identifier N0484094183.

Neuronetics international multi-centre trial

'Transcranial magnetic stimulation (TMS) in the treatment of major depression: an investigational clinical trial'. Commenced February 2005, and has been completed. A large, randomised, parallel group, sham-controlled, international multi-centre trial, sponsored by Neuronetics (with Australian involvement at centres in Sydney and Melbourne). A 6 month follow-on trial will be offered to all responders to evaluate the durability of the anti-depressant effects[3]. Results from the trial have been presented at the annual conference of the American Psychiatric Association (May 19-24, 2006, San Diego, USA). However, none of the results had been published in the public domain (searched on 2nd November 2006). The results have been submitted to the FDA for device approval in the USA.

Hansen PEB (senior physician), University of Aarhus, Denmark

'The antidepressant effect of rTMS compared to ECT. An open randomised study'. Expected completion October 2008, see ClinicalTrials.gov for more information, identifier NCT00299403.

[3] See www.med.monash.edu.au/spppm/research /aprc/tms-trial.html for more information

The above trial by McLoughlin and a Brazilian trial which published subsequent to the completion of this report and are discussed in Appendix H (Eranti et al 2007, Rosa et al 2006).

Recent health technology assessments and meta-analyses on rTMS

A list of electronic databases and websites of international HTA agencies can be found in Appendix F. The following studies and reviews were identified through searches of these databases, together with the main search strategy of this review:

Aarre TF, Dahl AA, Johansen JB, Kjonniksen I, Neckelmann D. Efficacy of repetitive transcranial magnetic stimulation in depression: A review of the evidence. *Nordic Journal of Psychiatry* 2003; **57**(3): 227-232.

Couturier JL. Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: A systematic review and meta-analysis. *Journal of Psychiatry & Neuroscience* 2005; **30**(2): 83-90.

Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: A meta-analysis. *International Journal of Neuropsychopharmacology* 2002; **5**(1): 73-103.

Holtzheimer PE, III, Russo J, Avery DH. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacol.Bull.* 2001; **35**(4): 149-169.

Kozel FA and George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *Journal of Psychiatric Practice* 2002; **8**(5): 270-275.

Kozel FA, George MS, Simpson KN. Decision analysis of the cost-effectiveness of repetitive transcranial magnetic stimulation versus electroconvulsive therapy for treatment of nonpsychotic severe depression. *CNS Spectrums* 2004; **9**(6): 476-482.

Loo CK and Mitchell PB. A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. *Journal of Affective Disorders* 2005; **88**(3): 255-267.

Martin J, Barbanoj MJ, Schlaepfer TE, Clos S, Perez V, Kulisevsky J, Gironell APR. Transcranial magnetic stimulation for treating depression (review). *The Cochrane Database of Systematic Reviews* 2001;(4).

Martin JL, Barbanoj MJ, Schlaepfer TE, Thompson E, Perez V, Kulisevsky J. Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis. *British Journal of Psychiatry* 2003; **182**: 480-491.

Mitchell PB and Loo CK. Transcranial magnetic stimulation for depression. *Australian & New Zealand Journal of Psychiatry* 2006; **40**: 406-413.

McNamara B, Ray JL, Arthurs OJ, Boniface S. Transcranial magnetic stimulation for depression and other psychiatric disorders. *Psychological Medicine* 2001; **31**(7): 1141-1146.

Ontario Health Technology Advisory Committee June 2004. 'Repetitive transcranial magnetic stimulation for the treatment of major depressive disorder'. Health technology literature review, and Recommendation (June 17 2004).

The National institute for Health and Clinical Excellence (NICE) in the UK have registered a review entitled 'Transcranial magnetic stimulation for severe depression' (September 2005). The review has been given a provisional publication date of late 2007.

Summary of the number of randomised controlled trials in the topic of depression

Table 8 shows that, according to various search strategies, there are relatively few published studies investigating the use of rTMS, or ECT, in depression. Expert opinion from the Advisory Panel suggests that one reason that there are so few studies investigating the effectiveness of ECT is that patients treated with sham ECT would also have to undergo general anaesthesia. In contrast, there are many more studies, and many more subjects, in trials investigating the effectiveness of pharmacotherapy for the treatment of depression. For example, there are 102 studies with over 10,000 participants in studies comparing two of the main types of drugs for depression. However, there appear to be many as yet unpublished trials concerned with rTMS and ECT, with numerous subjects.

Table 8 Summary of the number of RCTs in the topic of depression

Intervention	Number of trials	Number of patients	Comments
Published trials			
rTMS versus sham	54	1367	Systematic search
rTMS versus ECT	7	233	Systematic search
ECT versus sham	6	256	The UK ECT Review Group 2003
ECT versus drugs	13	760	The UK ECT Review Group 2003
Different ECT parameters	28	1347	The UK ECT Review Group 2003
SSRIs versus TCAs	102	10,706	From Anderson 2000
Unpublished trials			
rTMS versus ECT	2	245	Systematic search
rTMS versus sham	21	1,165	Systematic search
ECT versus [anything]	13	1,421	Systematic search

ECT: electroconvulsive therapy; rTMS: repetitive transcranial magnetic stimulation; SSRI: selective serotonin reuptake inhibitors; TCA: tricyclic anti-depressants

Expert advice

An advisory panel with expertise in psychiatry and depression was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the advisory panel is provided at Appendix B.

Results of assessment

Repetitive transcranial magnetic stimulation compared to ECT as a treatment for depression

Seven comparative studies were identified from the search strategy which compared rTMS with ECT as treatments for severe depression (Dannon et al 2002; Grunhaus et al 2000; Grunhaus et al 2003; Janicak et al 2002; O'Connor et al 2003; Pridmore et al 2000; Schulze-Rauschenbach et al 2005). All identified comparative studies were included in this review.

Of the published meta-analyses investigating the effectiveness of rTMS in the treatment of depression, most have analysed solely studies which compared rTMS with sham treatment (Martin et al 2003; Loo et al 2005; Aarre et al 2003; Holtzheimer et al 2001; Courturier 2005; McNamara et al 2001; Kozel & George 2002). The only published economic evaluation of rTMS versus ECT did not make a formal analysis of the effectiveness of both treatments (Kozel et al 2004). The Cochrane review on this topic (Martin et al 2001) conducted a meta-analysis of all rTMS studies; however, only one study comparing rTMS and ECT was available for review (Grunhaus et al 2000). The paper by Burt and colleagues (Burt et al 2002) was the only one to formally and independently analyse data comparing rTMS and ECT. Grunhaus et al 2000, Pridmore et al 2000 and Grunhaus et al (unpublished communication) were used, giving a combined weighted effects size (Cohen's *d*) of 0.21 favouring ECT, but with no statistically significant advantage of ECT over rTMS. In addition, they comment that the average percentage improvement with ECT was unusually low in these studies, so suggest that the therapeutic effect of ECT may have been underestimated. Also they surmise that, in comparison with sham rTMS data, extended rTMS treatment (four weeks as opposed to two weeks) provided greater anti-depressant properties, although very few studies had a four-week duration of treatment.

Critical appraisal of comparative studies

Table 9 and Table 10 summarise the quality of the comparative studies used in this review. The factors considered were based on the CONSORT Statement (Altman et al 2001). Dannon et al 2002 stands out from the other studies as study design information is very poorly reported. Three of the studies were randomised (Grunhaus et al 2000; Grunhaus et al 2003; Janicak et al 2002), although the exact methods of randomisation were not reported. Patients were not masked to the treatment method in any of the studies. Eligibility criteria was well defined in all the studies (other than Dannon et al 2002), and in general groups were well matched at baseline.

There was no recorded patient overlap between Grunhaus et al 2000, Grunhaus et al 2003, or Dannon et al 2002, although all these studies were all carried out in the same centre. Dannon et al 2002 may have been a long-term follow-up of some of the patients reported in Grunhaus et al 2000, although this was not stated. Grunhaus et al 2003 only included non-psychotic patients, whereas Grunhaus et al 2000 included both psychotic and non-psychotic patients.

Table 9 Critical appraisal summary of comparative studies – study design details

Study	Randomisation details	Blinding	Sample size	Participants	Interventions and outcomes
Pridmore et al 2000	Randomised according to order of presentation	Patients were not masked	n = 32 patients	Eligibility criteria defined Groups well matched at baseline	Details of interventions provided Primary outcomes defined No limit to ECT treatment
Grunhaus et al 2000	No details of randomisation, concealment or implementation	Patients were not masked No masking procedure used	n = 40 patients Power analysis not performed as this was a preliminary study	Extensive eligibility criteria Groups well matched at baseline	Details of interventions provided Primary outcomes defined Response defined 'a priory'
Dannon et al 2002	NR	NR	n = 40 patients	NR	NR
Grunhaus et al 2003	No details of randomisation, concealment or implementation	Patients were not masked Raters masked, no details of this procedure	n = 40 patients	Extensive eligibility criteria Groups well matched at baseline other than patients in the ECT group had significantly worse BPRS and GAF scores, were older (NS), with more inpatients (NS)	Details of interventions provided Primary outcomes defined Response defined 'a priory' No limit to ECT treatment
Janicak et al 2002	No details of randomisation, concealment or implementation	Patients were not masked Masking of raters NR. Intra-class coefficient among raters was 0.958	n = 25 patients	Extensive eligibility criteria Groups well matched at baseline	Details of interventions provided Primary outcomes defined Response defined 'a priory'
O'Connor et al 2003	Non-randomised	Patients were not masked Raters were not blinded	n = 28 patients	Extensive eligibility criteria Groups well matched at baseline other than patients in ECT group had a significantly higher HDRS score	Details of interventions provided Primary outcomes defined
Schulze-Rauschenbach et al 2005	Non-randomised consecutive cases. Patient was allowed choice of treatment if no exclusion criteria were present	Patients were not masked Raters were masked	n = 30 patients	Extensive eligibility criteria Groups well matched at baseline	Details of interventions provided Primary outcomes defined Response defined 'a priory'

- based on the Consort Statement (Altman et al 2001); NR: not reported

Table 10 Critical appraisal summary of comparative studies – results details

Study	Numbers analysed	Statistical methods	Outcomes and estimation	Ancillary analyses	Adverse events	Follow-up
Pridmore et al 2000	Intention-to-treat and per-protocol analysis not defined	Tests detailed Significance level defined	Results for each outcome detailed	No subgroup analyses performed	Detailed for both groups (using an 'in-house' side effect scale)	Final outcome recorded at exit from the study No losses
Grunhaus et al 2000	Intention-to-treat and per-protocol analysis not defined	Tests detailed Significance level defined	Results for each outcome detailed Chi-squared reported	Subgroup analyses performed post-hoc for psychotic and non-psychotic patients	Recorded for rTMS but not for ECT	Final outcome recorded at end of treatment No losses
Dannon et al 2002	NR	Tests detailed Significance level defined	Results for each outcome detailed CIs reported	No subgroup analyses performed	NR	3 and 6 months 2 patients lost from rTMS group
Grunhaus et al 2003	Intention-to-treat and per-protocol analysis not defined	Tests detailed Significance level defined	Results for each outcome detailed CIs reported	Subgroup analyses performed for responders	Recorded for rTMS but not for ECT	Final outcome recorded at end of treatment No losses
Janicak et al 2002	Intention-to-treat and per-protocol analysis not defined	Tests detailed Significance level defined	Results for each outcome detailed	No subgroup analyses performed	Recorded in detail for rTMS, less detail for ECT	Final outcome recorded at end of treatment 2 patients lost from each group
O'Connor et al 2003	Intention-to-treat and per-protocol analysis not defined	Tests detailed Significance level defined	Results for each outcome detailed	No subgroup analyses performed	NR	2 weeks No losses
Schulze-Rauschenbach et al 2005	Intention-to-treat and per-protocol analysis not defined	Tests detailed Significance level defined	Results for each outcome detailed	No subgroup analyses performed	NR	1 week 1 patient lost from ECT group

- based on the Consort Statement (Altman et al 2001); ECT: electroconvulsive therapy; NR: not reported; rTMS: repetitive transcranial magnetic stimulation

Baseline study characteristics

Baseline characteristics of patients are listed in Table 11. The total numbers of patients which completed the studies was 233. Of these, the majority of subjects were female (131 females and 78 males were reported to have taken part), and the majority suffered from unipolar depression (103, compared with 34 bipolar, where reported). There was a variety in the continuation of pharmaceutical treatments between the two study groups in three studies (Grunhaus et al 2000; Janicak et al 2002; O'Connor et al 2003) where patients treated with rTMS were removed from medication, whilst ECT patients remained on medication (Table 12, Table 13).

Table 11 Patient characteristics at baseline

Study	Intervention group	Number of patients (start/end)	Age (mean years, sd)	Gender (M/F)	HDRS scores (mean, sd)	Unipolar / bipolar	Psychotic / non-psychotic	History of previous ECT (N/Y)	
Pridmore et al 2000	rTMS	16/16	44.0, 11.9	4/12	25.3, 4.1	11/5	NR	10/6	P=0.25, ns
	ECT	16/16	41.5, 12.9	3/13	25.8, 3.6	15/1	NR	13/3	
Grunhaus et al 2000	rTMS	20/20	58.4, 15.7	8/12	25.6, 6.1	14/6 (axis II)	9/11	14/6	P=0.4, ns
	ECT	20/20	63.6, 15	6/14	28.4, 9.3	18/2	10/10	11/9	
Dannon et al 2002	rTMS	23/21	56.9, 15.3	6/14	NR	NR	2/18	12/8	P=ns
	ECT	20/20	57.4, 16.7	7/14	NR	NR	6/14	13/8	
Grunhaus et al 2003	rTMS	20/20	57.6, 13.7	6/14	24.4, 3.9	13/7 (axis II)	None	12/8	P=1.0, ns
	ECT	20/20	61.4, 16.6	5/15	25.5, 5.9	15/5	None	15/5	
Janicak et al 2002	rTMS	15/13	42.9, 12.9	11/4	32.2, 6.8	10/4	3/12	NR	P=ns
	ECT	11/9	42.7, 14	6/5	31.4, 8.5	7/4	6/5	NR	
O'Connor et al 2003	rTMS	14/14	51.2, 12.2	NR	29.3, 4.9	NR (no axis I)	None	NR	NR
	ECT	14/14	48.4, 12	NR	38.1, 8.1	NR	None	NR	
Schulze-R et al 2005	rTMS	16/16	47.7, 13.1	9/7	21.3, 3.5	NR (no axis I)	None	NR	NR
	ECT	14/14	46.7, 11	7/7	22.3, 3	NR	None	NR	
TOTAL	14 groups	233 (end)		78/131		103/34			
MEAN		16.6		6.5/10.9		12.9/4.3			
MEDIAN [RANGE]			49.8 [41.5-63.6]		25.7 [21.3 – 38.1]				

ECT: electroconvulsive therapy; rTMS, repetitive transcranial magnetic stimulation; sd: standard deviation; M; male; F: female; HDRS: Hamilton depression rating scale; NR: not reported; ns: not significant

Technical information of rTMS and ECT settings used in the studies are listed in Tables 12 and 13. As can be seen, there is marked similarity between rTMS treatment modalities in all the included studies (Table 12). All rTMS treatments are unilaterally to the left dorsolateral cortex, with stimulation at around 100 per cent motor threshold (range 90-110%) and of high frequency (10-20Hz). The total number of pulses per second was also similar, and similarly distributed between

train duration, interval, and train number. Studies were slightly more varied in their modes of ECT treatment (Table 13). Although anaesthesia, muscle relaxation and level of oxygenation were, when reported, similar between studies, stimulation varied with regard to side of treatment (unilateral, bilateral or mixed) and seizure length (4.8-32.4 sec).

Table 12 Repetitive transcranial magnetic stimulation technical information

Study	Medications*	Uni/bilateral, side	Intensity (% motor threshold)	Frequency (Hz)	No. trains per session	Duration (sec)	Interval (sec)	Total pulses per session	Treatment per week	Total No. treatments	Number of weeks of treatment	Session duration (mins)
Pridmore et al 2000	None	U, Left	100	20	33	2	28	1320	5	12.2 sd 3.4	NR	16.5
Grunhaus et al 2000	None	U, Left	90	10	20	2 or 6	NR	400 or 1200	5	20	4	NR
Dannon et al 2002	Yes	U, Left	90	10	20	6	30	1200	5	20	4	12.0
Grunhaus et al 2003	None	U, Left	90	10	20	6	30	1200	5	20	4	12.0
Janicak et al 2002	None	U, Left	110	10	20	5	25	1000	5	13	2-4	10.0
O'Connor et al 2003	None	U, Left	90	10	20	8	24	1600	5	10	2	10.7
Schulze-R et al 2005	Yes	U, Left	100	10	25	2	5	500	2–3	10.8 sd 1.4	NR	2.9

NOTE * - were the subjects washed out from psychotropic medications prior to the trial (None), or did they continue with drugs throughout the trial (Yes)?
NR: not reported; sd: standard deviation

Table 13 Electroconvulsive therapy technical information

Study	Medications*	Uni/bilateral, side	Anaesthesia	Muscle relaxation	Oxygenation	Dosage (seizure threshold)	Seizure length (sec)	No. treatments per week	Total No. treatments
Pridmore et al 2000	None	U, ND	1-1.5mg/kg MH	0.5mg/kg SUXA	Yes	NR	NR	3	6.2 sd 1.6
Grunhaus et al 2000	Yes	12/8	1mg/kg MH	0.75-1mg/kg SUC	100%	2.5x	≥25 sec	NR	9.6
Dannon et al 2002	Yes	M	0.75-1mg/kg MH	0.5-1mg/kg SUC	NR	2.5x	≥25 sec	NR	NR
Grunhaus et al 2003	None	13/7	1mg/kg MH	0.75-1mg/kg SUC	100%	2.5x	32.4 sd 7.8	NR	10.3 sd 3.1
Janicak et al 2002	Mixed	Bi-temporal	1mg/kg MH	1mg/kg SUC	100%	NR	4.8 sd 13.3	3	9
O'Connor et al 2003	Yes	U, Right	NR	NR	NR	2.5x	NR	3	2
Schulze-R et al 2005	Yes	U, Right	2mg/kg propofol	1mg/kg SUXA	100%	2-2.5x	NR	2	9.9 sd 2.7

M = mixed; ND = non-dominant hemisphere; MH = methohexitone; NR: not reported; SUXA = suxamethonium; SUC = succinylcholine

Is it safe?

Table 14 Adverse event outcomes for rTMS and ECT from the comparative studies

Study		Adverse events	How were the events reported
Pridmore et al 2000	rTMS	Entry – 8.1 (sd 3.2); Exit – 3.9 (sd 2.9)	A four-point severity scale*
	ECT	Entry – 6.1 (sd 3.6); Exit – 5.3 (sd 4.3)	
	p-value	NS at entry, and exit	
Grunhaus et al 2000	rTMS	Mild headache (n=5); MEP discharge (n=1)	Numbers of patients reported
	ECT	NR (no patient had treatment interrupted due to side effects)	
Dannon et al 2002	rTMS	NA; relapse (n=4)	-
	ECT	NA; relapse (n=4)	
Grunhaus et al 2003	rTMS	Mild headache (n=3); sleep disturbance (n=2)	Numbers of patients reported (using an open-ended questionnaire)
	ECT	NR (no patient had treatment interrupted due to side effects)	
Janicak et al 2002	rTMS	Seizures (n=0); erythema at site of coil placement (n=6); mild pain or discomfort (n=6); feelings of warmth (n=3); tapping like hammer sensation (n=2); headache (n=1); moderate pain at site of treatment (n=1)	Numbers of incidence reported
	ECT	Bitemporal ECT caused short-term memory impairment (n=NR); drowsiness shortly after treatment (n=NR)	
O'Connor et al 2003	rTMS	NR	-
	ECT	NR	
Schulze-R et al 2005	rTMS	NR	-
	ECT	NR	

* - Adverse events recorded using a 7-item rating scale developed especially for this study (for memory problems, headache, muscle stiffness, dry mouth or blurred vision, nausea abdominal discomfort or bowel problems, tremor, weakness tiredness or sleepiness, on a 4-point severity scale.

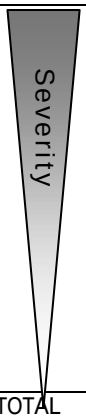
ECT: electroconvulsive therapy; MEP: motor electrode potential; NA: not applicable; NR: not reported; rTMS: repetitive transcranial magnetic stimulation;

In the 7 comparative studies, adverse events are poorly recorded for the ECT groups (Table 14), with the exception of Pridmore et al 2000, who used a specially developed adverse events scale (see footnote below Table 14). For Pridmore et al 2000, although the adverse events score favoured patients treated with ECT at entry in the study, this score favoured rTMS at exit, suggesting that rTMS was the more favourable treatment once patients become accustomed to the regime. However, there was no statistically significant difference between the scores of each group at entry, or at exit, from the study (p=NS). Dannon et al 2002, O'Connor et al 2003 and Schulze-Rauschenbach et al 2005 do not record adverse events for rTMS or ECT treatment. Grunhaus et al 2000 and Grunhaus et al 2003 did not record adverse events for ECT, but merely stated that 'no patient had treatment disrupted due to side-effects'. Janicak et al 2002 recorded adverse events in full for rTMS, but reported adverse events in the absence of patient numbers for ECT.

Table 15 summarises the data collected from the non-comparative studies included in this review. Of a total of 1698 patients treated with rTMS, there were a total reported number of 258 cases of adverse events. The majority of these were relatively mild, with side-effects such as cognitive impairment, auditory problems, headaches, mild pain and other transient events constituting 237 of the 258 cases (92%). The more serious side effects are reported in more detail in Table 16 and Table 17.

Table 15 Adverse events for rTMS from the non-comparative studies (level II, III and IV)

		TOTAL	Median	Range
Number of studies		121		
rTMS treatments		151		
Number of patients		1698		
Male		579		
Female		886		
Type of major depression (per rTMS treatment)	Unipolar	20		
	Bipolar	12		
	Mixed	53		
	Psychotic	2		
	NR	64		
Age (years)			46.8	21–67.9
Pre-treatment depression scores	Hamilton score		25.9	16–37.2
	Beck depression inventory		28.9	27–48
Concurrent medication (per rTMS treatment)	Yes	67		
	No	29		
	Mixed	37		
	NR	18		
Unilateral / bilateral (per rTMS treatment)	Unilateral	142		
	Bilateral	9		
Left hand side	Total (per rTMS treatment)	121		
	Frequency		10Hz	0.25–20Hz
	Stimulation intensity		100% MT	53–130% MT
	No. trains per session		20	1–100
	Interval		30 sec	1–60 sec
	Duration		5 sec	2–1600 sec
Right hand side	Total (per rTMS treatment)	30		
	Frequency		1Hz	0.25–15Hz
	Stimulation intensity		110% MT	25–130% MT
	No. trains per session		5	1–100
	Interval		60 sec	4–180 sec
	Duration		60 sec	5–1200 sec
Treatment duration			14 days	4–42 days
Treatment frequency			5 per week	1–5 per week
Total number of treatments			10	3–280
Adverse outcomes				
1	Death, including suicide	0		
2	Seizures	4		
3	Psychosis	4		
4	Mania	11		
5	Neurological impairment	2		
6	Cognitive impairment	5		
7	Auditory problems	1		
8	Headaches	125		
9	Mild pain	61		
10	Other transient	45		
11	Technical complications	0		
TOTAL		258		



ECT: electroconvulsive therapy; MT: motor threshold; NR: not reported; rTMS: repetitive transcranial magnetic stimulation.

Table 16 Details of the major adverse events of rTMS reported in the non-comparative studies - patient presentation

Patient presentation	Level of evidence	No. of events	Age mean (sd)	Gender	HDRS score	Uni/bipolar	Medications	Comments
SEIZURES								
Epstein 1998	IV (cs)	1	46	F	>20	M	M	Left focal motor seizure; no previous history
Conca 2000	IV (cr)	1	36	F	NR	NR	Y	Patient had previously suffered a maprotiline-induced seizure
Pikryl 2005	IV (cr)	1	45	M	NR	NR	N	2 night's sleep deprivation; patient was otherwise healthy
Tharayil 2005	IV (cr)	1	35	M	NR	B	Y	Family history of seizure
PSYCHOSIS								
Conca 2002	II	2	47 (10)	NR	>24	M	Y	No patient-specific details given
Shajahan 2002	II	1	37 (14)	NR	21	NR	M	No patient-specific details given
Zwanger 2002	IV (cr)	1	55	M	NR	NR	N	No family incidence of psychosis. Symptoms ceased when rTMS ceased
MANIA								
Hausmann 2004 (a)	II	(1)	-	-	-	-	-	Reported fully in Hausmann 2004 (b)
Su 2005	II	(1)	-	-	-	-	-	Reported fully in Huang 2004
Dolberg 2001	IV (cr)	2	46, 54	1F, 1M	NR	B	Y	Two case reports
Ella 2002	IV (cr)	2	79, 46	1F, 1M	32	B	Y	Two case reports
Garcia-Toro 1999	IV (cr)	1	44	M	31	B	Y	20-year history of bipolar disorder
Hausmann 2004 (b)	IV (cr)		45 (12)	F	32.9	B	Y	Symptoms ceased when rTMS ceased
Huang 2004	IV (cr)	1	43	F	NR	B	Y	8-year history of bipolar disorder with 2 episodes
Sakkas 2003	IV (cr)	2	55, 46	2M	25, 30	U, B	Y	Both patients remained on medications and had intensive rTMS (twice a day)
NEUROLOGICAL IMPAIRMENT								
Epstein 1998	IV (cs)	2	51, 44	2F	>20	M	M	Left side paresthesia; motor tics
Figiel 1998	IV (cs)	(2)	-	-	-	-	-	Reported in Epstein 1998

cs = case series; cr = case report; M = mixed (some patients on medications, some not on medications); NR: not reported F: female; M: male; B: bipolar; U: unipolar; Y = patients remained on medication during treatment; N = patients were removed from medication prior to treatment.

Table 17 Details of the major adverse events of rTMS reported in the non-comparative studies - technical information

Technical information	Level of evidence	Uni/bilateral	Intensity (%MT)	Frequency (Hz)	No. trains per session	Duration (sec)	Interval (sec)	Total pulses per session	Treatments per week	Total no. treatments	No. weeks treatment
SEIZURES											
Epstein 1998	IV (cs)	U, L	110	10	10	5	30	500	5	5	1
Conca 2000	IV (cr)	U, L	110	20	10	10	60	2000	5	5	1
Pikryl 2005	IV (cr)	U, L	110	15	NR	10	30	NR	5	6	1.5
Tharayil 2005	IV (cr)	U, L	58	NR	NR	NR	NR	NR	NR	NR	NR
PSYCHOSIS											
Conca 2002	II	U, L	110	10	13	10	NR	1300	5	5	1
Shajahan 2002	II	U, L	80	5	25	4	60	500	5	10	2
Zwanger 2002	IV (cr)	U, L	100	10	15	10	30	1500	5	13	3
MANIA											
Hausmann 2004 (a)	II	(see Hausmann 2004(b))									
Su 2005	II	U, L	100	20, 5	-	-	-	-	-	-	-
Dolberg 2001	IV (cr)	NR	NR	10	20	6	30	1200	5	20	4
Ella 2002	IV (cr)	U, R	110	1	NR	NR	NR	NR	5	10-15	2-3
Garcia-Toro 1999	IV (cr)	U, L	90	20	30	2	30	1200	5	10	2
Hausmann 2004 (b)	IV (cr)	B	100 L, 120 R	20, 1	10, 1	10, 600	90, -	600 - 2000	5	7 (of 10)	2
Huang 2004	IV (cr)	U, L	100	5	40	8	NR	1600	3	3	1
Sakkas 2003	IV (cr)	NR	NR	NR	NR	NR	NR	NR	6-10	28-30	3-6
NEUROLOGICAL IMPAIRMENT											
Epstein 1998	IV (cs)	U, L	110	10	10	5	30	500	5	5	1
Figiel 1998	IV (cs)	U, L	110	10	10	5	30	500	5	5	1

cs = case series; cr = case report; M = mixed (some patients on medications, some not on medications); MT: motor threshold; NR: not reported F: female; M: male; B: bipolar; U: unipolar.

Tables 16 and 17 show that in general, there are few factors in common between any of the four major adverse events shown, either with regard to patient presentation or technical characteristics. There was one exception, namely that most patients (6/7) who suffered a manic episode originally presented with bipolar depression (Table 16).

Cognitive outcomes

Table 18 Cognitive outcomes reported by the comparative studies

Study	Test with no significant difference between rTMS and ECT (p=NS at end of treatment)	Test with a significant difference between rTMS and ECT (p<0.05 at end of treatment) All changes were improvements for patients treated with rTMS
Grunhaus et al 2000	■ Mini mental status examination	
O'Connor et al 2003		Working memory ■ Letter number sequencing, LNS New learning Acquisition ■ Rey Auditory verbal learning test (RVLT) ■ Retention – RVLT Retrograde memory ■ Transient news events test (TNET)
Schulze-Rauschenbach et al 2005	Learning and anterograde memory; AVLT (Auditory verbal learning test): ■ Immediate recall ■ Recognition hits ■ Recognition false alarms MPT (memory for person test): ■ Recall trial 3 ■ Delayed recall Retrograde memory Retrograde AVLT ■ Recall ■ Recognition hits Four-card task ■ Recognition AMI (autobiographical memory interview) ■ Recall score ■ MMSE (Mini-mental state exam) ■ Trail making test A ■ Trail making test B ■ Digit span (WAIS-R, Wechsler adult intelligence scale) ■ Letter-number span ■ Word fluency (LPS, Leistungs-Pruf-System)	■ Recall after interference ■ Recall after delay ■ Recognition false alarms ■ Free recall Subjective memory ■ SSMQ (Squire subjective memory questionnaire)

NOTE ■ – indicates the implemented test; ECT: electroconvulsive therapy; rTMS: repetitive transcranial magnetic stimulation.

Three studies used various tests to investigate cognitive effects of rTMS and ECT during the treatment of depression (Table 18). Grunhaus et al 2000 used the Mini Mental Status

Examination (MMSE). No data was reported, but the authors state that there was no significant difference between the outcomes of the two groups. O'Connor et al 2003 and Schulze-Rauschenbach et al 2005 were both mainly concerned with investigating rTMS and ECT effects on cognitive function, rather than on the treatment of depression. All tests used in O'Connor et al 2003 showed that treatment with rTMS had significantly better outcomes for cognitive function than treatment with ECT (Table 18 and Table 19). O'Connor et al 2003 also reported cognitive outcomes at a follow-up of two weeks, at which point ECT scores had recovered and were not significantly different from rTMS scores for all tests (not shown). Most of the cognitive tests used by Schulze-Rauschenbach et al 2005 showed no significant difference between the rTMS group and ECT group at the end of treatment (Table 18 and Table 19). Tests that were shown to be significantly different between each group are shown in Table 19. All favoured rTMS over ECT. Interestingly, subjective memory (SSMQ test, Table 19) was improved from baseline in both rTMS and ECT groups, showing that patients considered depression itself to have a negative effect on memory, and that treatment with ECT did not impair memory, but improved it.

Table 19 Cognitive outcomes from the comparative studies

Cognitive function	% change at end of treatment (All changes were improvements for patients treated with rTMS)				P value
	O'Connor et al 2003		Schulze-Rauschenbach et al 2005		
	rTMS	ECT	rTMS	ECT	
Working memory (LNS)	Pre 10.4 (3.0) Post 10.7 (3.8) +2.8%	Pre 10.9 (2.5) Post 9.2 (1.8) -15.6%			NS at baseline NS between groups at end
New learning – acquisition	Pre 43.7 (12.1) Post 43.0 (10.1) -1.6%	Pre 43.8 (11.1) Post 29.1 (7.9) -33.6%			NS at baseline <0.01 between groups
New learning – retention	Pre 9.8 (3.1) Post 8.2 (2.8) -16.3%	Pre 8.1 (4.5) Post 2.1 (2.0) -74.1%			NS at baseline <0.01 between groups
Retrograde memory – TNET	Pre 55.6 (18.2) Post 57.8 (18.3) +3.8%	Pre 64.3 (19.4) Post 39.1 (13.2) -39.2%			NS at baseline <0.01 between groups
Learning and anterograde recall after interference			Pre 3.2 (1.9) Post 1.8 (2.0) -43.8%	Pre 2.8 (2.2) Post 3.9 (1.9) +39.3%	NS at start <0.01 between groups at end
Learning and anterograde recall after delay			Pre 3.2 (1.6) Post 2.4 (2.0) -25%	Pre 2.4 (1.8) Post 4.2 (1.6) +75%	NS at start <0.05 between groups at end
Retrograde AVLT recognition false alarms			No baseline; 1.1 (1.1) post	No baseline; 5.0 (3.0) post	<0.05 at end
Four card task free recall			No baseline; 1.4 (1.2) post	No baseline; 0.4 (0.5) post	<0.05 at end
Subjective memory (SSMQ)			Pre -16.8 (16.9) Post 3.8 (11.8) +122.6%	Pre -20.7 (19.0) Post -15.2 (25.2) +26.6%	NS at start <0.01 between groups at end

ECT: electroconvulsive therapy; NS: not significant; rTMS: repetitive transcranial magnetic stimulation.

Further information regarding description of the cognitive tests used by O'Connor et al 2003 and Schulze-Rauschenbach et al 2005 can be seen in Table 46, Appendix E.

Is it effective?

Outcomes measured as response to treatment

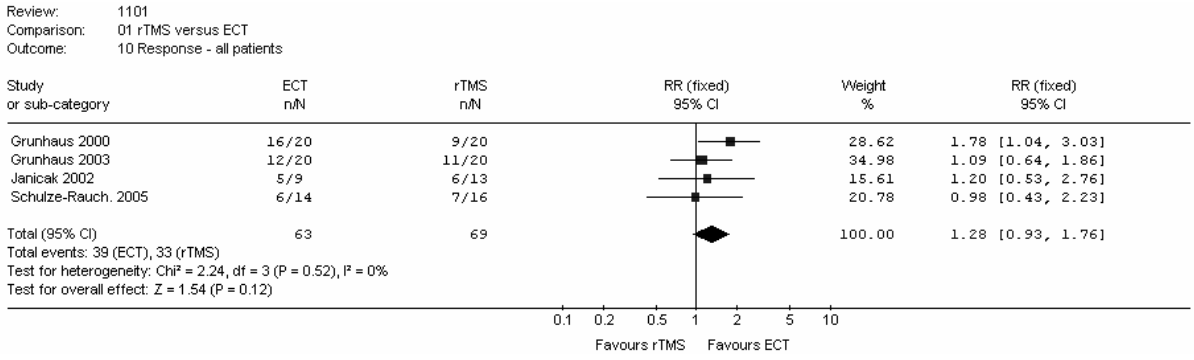
Four comparative studies gave a definition of response to treatment 'a priori' (Table 20), mainly based on a specified reduction in the outcome as measured using the Hamilton rating scale for depression (HDRS, Table 40 Appendix E). The results are displayed in Figure 2, and show that a greater number of patients responded to ECT treatment for depression, although this difference is not statistically significant (p=0.12). The weighting for each study is based solely on the number of participants in the study as a proportion of the total number of participants.

Table 20 Number and proportion of patients who responded to rTMS and ECT treatment

	Responders (Y/N, %)			Definition of response
	rTMS	ECT	P-value	
Grunhaus et al 2000	9/11 (45%)	16/4 (80%)	P<0.05 (overall)	Final HDRS decreased by 50% or more from baseline and final GAF>=60
Grunhaus et al 2003	11/9 (55%)	12/8 (60%)	NS	Final HDRS decreased by 50% or more from baseline or final HDRS <=10, final GAF>=60
Pridmore et al 2000	NR	NR	-	-
Janicak et al 2002	6/7 (46%)	5/4 (56%)	NS	Final HDRS decreased by 50% or more from baseline and final HDRS score <=8
Schulze-R et al 2005	7/9 (44%)	6/8 (46%)	P=0.9, NS	Final HDRS decreased by 50% or more from baseline
O'Connor et al 2003	NR	NR	-	-
MEAN	48%	62%	-	-

ECT: electroconvulsive therapy; NR: not reported; NS: not significant; rTMS: repetitive transcranial magnetic stimulation

Figure 2 Meta-analysis showing patient response to treatment with either rTMS or ECT



Hamilton depression rating scores

The Hamilton depression rating scale (HDRS), a clinician-rated scale of depression, has been used in all the comparative studies as the main measure of depression, and was therefore the main clinical outcome (Table 40, Appendix E). HDRS scores are listed in Table 21, and have also been represented in Figure 3, Figure 4 and Figure 5. Dannon et al 2002 did not report baseline data for any outcome, therefore the effect of treatment with rTMS or ECT on the severity of depression could not be determined. The effect size (ie the difference between baseline and end of treatment) and percentage improvement has been calculated for each study, where possible (Table 21), although as these were not reported in any of the studies these figures have no associated distribution.

Baseline HDRS scores favour patients in the rTMS group (Figure 3), but at the end of a four-week treatment regime HDRS scores favour ECT (Figure 5), although the differences are not significant (p=0.2 and 0.29 respectively). After two weeks of treatment, HDRS scores show that rTMS and ECT are equi-effective in the treatment of depression (Figure 4, results from two studies). Although it was not possible to meta-analyse the effect size of treatment, there is a possibility that the effect size of ECT may have approached significance over the effect size of rTMS. The weighting in these analyses took into account the standard distribution as well as the total number of participants of each study.

Figure 3 Baseline HDRS scores, rTMS versus ECT

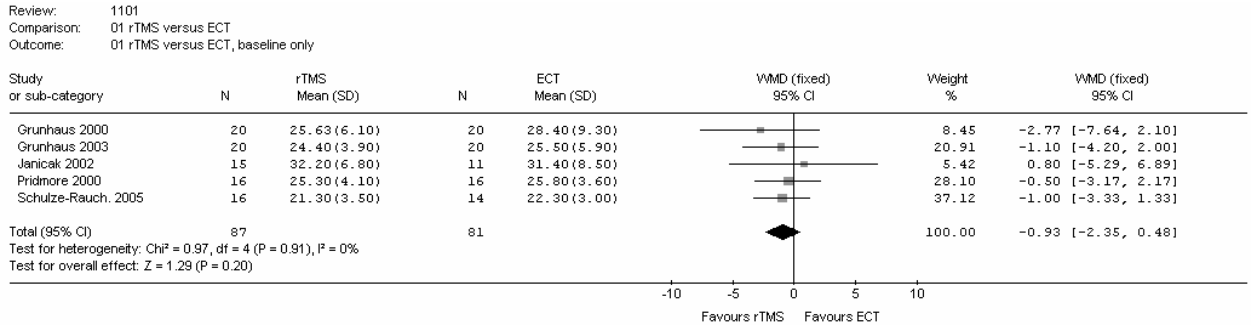


Figure 4 Two week HDRS scores, rTMS versus ECT

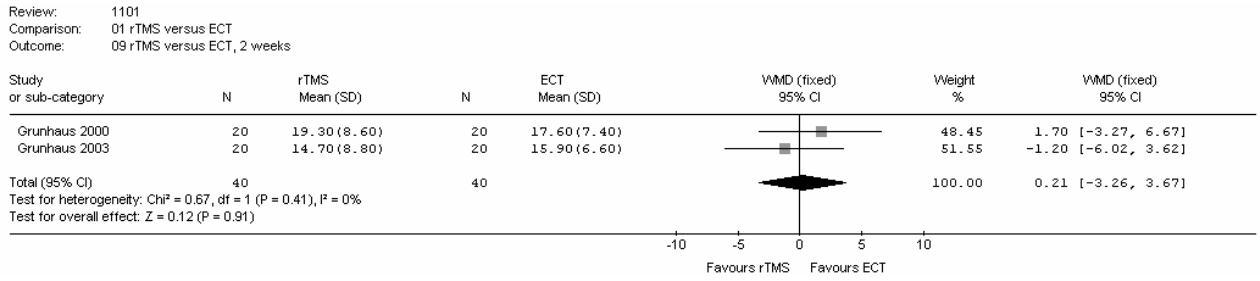


Figure 5 Four week HDRS scores (end of treatment outcomes), rTMS versus ECT

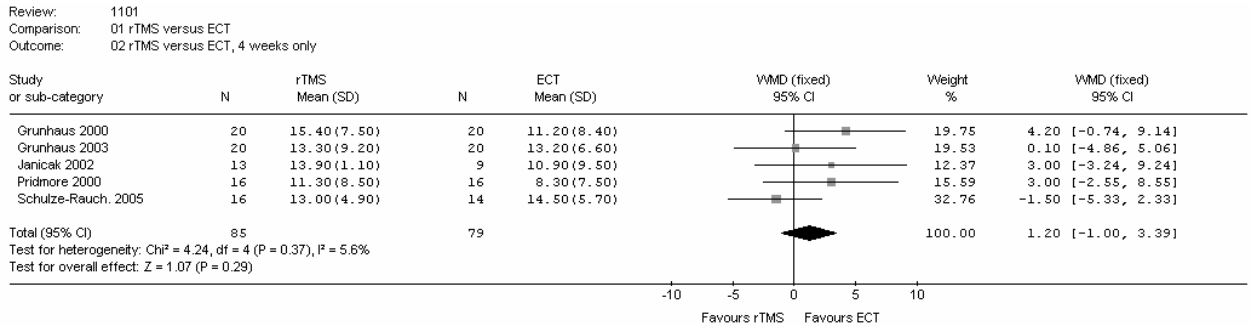


Table 21 Hamilton depression rating scale scores

Study		Baseline Mean (SD)	Week 2 Mean (SD)	End of treatment Mean (SD)	Effect size (% improvement)	Follow-up Mean (SD) [time]
Pridmore et al	rTMS	25.3 (4.1)	-	11.3 (8.5)	14.0 (55.3%)	-
2000	ECT	25.8 (3.6)	-	8.3 (7.5)	17.5 (67.8%)	-
	p-value	NS (f)		NS (f)	-	-
Grunhaus et al 2000	rTMS	25.8 (6.1)	19.3 (8.6)	15.4 (7.5)	10.4 (40.3%) (week 4)	-
	ECT	28.4 (9.3)	17.6 (7.4)	11.2 (8.4)	17.2 (60.6%) (week 4)	-
	p-value	NS (a)		NS (a)	-	
Dannon et al	rTMS	NR	-	7.8 (3.7)	NA	6.4 (4.9) [3 month]; 7.9 (7.1) [6 month]
2002	ECT	NR	-	7.9 (4.5)	NA	7.7 (5.0) [3 month]; 8.4 (5.6) [6 month]
	p-value	-		NS (e)	-	NS (e)
Grunhaus et al 2003	rTMS	24.4 (3.9)	14.7 (8.8)	13.3 (9.2)	11.1 (45.5%) (week 4)	-
	ECT	25.5 (5.9)	15.9 (6.6)	13.2 (6.6)	12.3 (48.2%) (week 4)	-
	p-value	NS (g)		NS (g)	-	-
Janicak et al	rTMS	32.2 (6.8)	-	13.9 (1.1)	18.3 (56.8%)	-
2002	ECT	31.4 (8.5)	-	10.9 (9.5)	20.5 (65.2%)	-
	p-value	NS (d)		NS (d)	-	-
O'Connor et al 2003	rTMS	29.3 (4.9)	25.6 (7.7)	-	3.7 (12.6%) (week 2)	24.8 (9.5) [2 week]
	ECT	39.0 (7.3)	15.3 (11.7)	-	23.7 (60.8%) (week 2)	20.4 (9.5) [2 week]
	p-value	<0.01 (c)	NS (c)		-	NS (c)
Schulze-R et al	rTMS	21.3 (3.5)	-	13.0 (4.9)	8.3 (39.0%)	-
2005	ECT	22.4 (3.1)	-	14.5 (5.7)	7.9 (35.3%)	-
	p-value	NS (b)		NS (b)	-	-

(a) Analysis of variance (ANOVA) with repeated measures, with additional post hoc analysis performed with two-sample t tests and chi-squares. (b) Analysis of variance (ANOVA) with repeated measures, between-group t-tests (Welch-corrected for unequal variances) and within-group t-tests. (c) 2x3 repeated measure analysis of variance (ANOVA). Baseline group differences on the mood ratings and cognitive tasks were compared with unpaired t-tests. (d) Paired samples t test comparing baseline to end of treatment ratings was computed for each group. (e) t tests for continuous measures and chi squares for dichotomous variables. (f) Repeated-measure ANOVAs. (g) Baseline comparisons performed with either two-sample t-tests for continuous data or chi-squared for nominal data. Repeated-measure analysis of variance (ANOVA) for change of score with treatment. Final ratings were analysed with Student's t-test.

Beck depression inventory scores

The Beck depression inventory (BDI) is a common scale for measuring the severity of depression, but differs from the HDRS in being a patient-rated, not clinician-rated scale. Clinical outcomes of the BDI are shown in Table 22.

Table 22 Beck depression inventory scores

Study		Baseline Mean (SD)	Week 2 Mean (SD)	End of treatment Mean (SD)	Effect size (% improvement)	Follow-up
Pridmore et al	rTMS	33.9 (6.8)	-	19.2 (11.8)	43.4	-
2000	ECT	31.8 (6.6)	-	9.6 (8.9)	69.8	-
	p-value	NS	-	0.01	-	-

ECT: electroconvulsive therapy; NS: not significant; rTMS: repetitive transcranial magnetic stimulation.

When depression severity was measured on the BDI scale (Table 22), ECT treatment gave a significantly better clinical outcome than rTMS. However, the BDI was only used in one study (Pridmore et al 2000), and is a patient-rated questionnaire which rates feelings of depression. (See Table 41, Appendix E for a full description of the BDI).

Brief psychiatric rating scale scores

The brief psychiatric rating scale (BPRS) is a 24-item observer scale designed to assess patients with major psychiatric disorders. BPRS outcomes are shown in Table 23.

Meta-analysis of the data shown in Table 23 shows that, at baseline, BPRS scores were significantly lower for the rTMS patients (p=0.03, Figure 6). In contrast, at the end of the treatment (four weeks, Figure 7), BPRS scores favour ECT patients, although this difference is not statistically significant (p=0.29). (The BPRS is explained in Table 42, Appendix E).

Figure 6 Meta-analysis of brief psychiatric rating scale scores at baseline

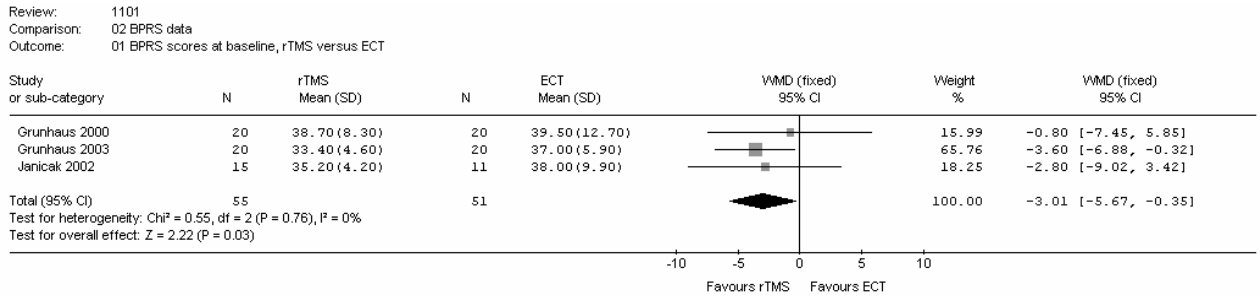


Figure 7 Meta-analysis of brief psychiatric rating scale scores at four weeks

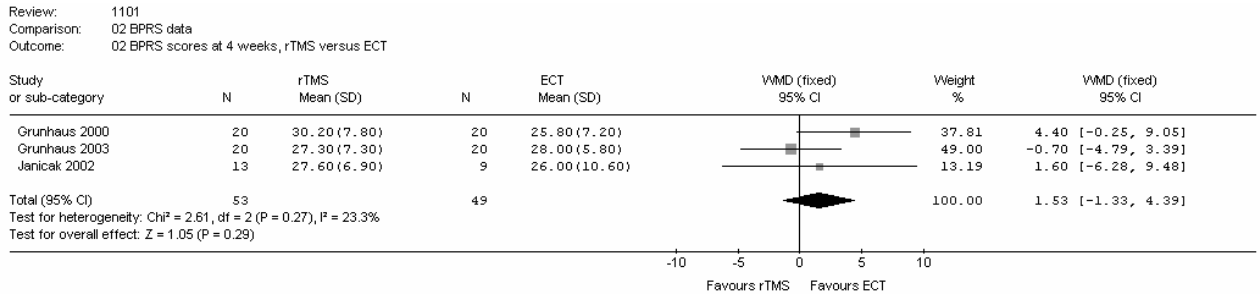


Table 23 Brief psychiatric rating scale scores

Study		Baseline Mean (SD)	Week 2 Mean (SD)	End of treatment Mean (SD)	Effect size (% improvement)
Pridmore et al	rTMS	-	-	-	
2000	ECT	-	-	-	
	p-value				
Grunhaus et al	rTMS	38.7 (8.3)	33.6 (7.2)	30.2 (7.8)	22.0
2000	ECT	39.5 (12.7)	32.0 (8.8)	25.8 (7.2)	34.7
	p-value	NS	NS	NS	-
Dannon et al	rTMS	-	-	-	
2002	ECT	-	-	-	
	p-value				
Grunhaus et al	rTMS	33.4 (4.6)	28.8 (6.9)	27.3 (7.3)	18.3
2003	ECT	37.0 (5.9)	31.2 (6.0)	28.0 (5.8)	24.3
	p-value	NS	NS	NS	-
Janicak et al	rTMS	35.2 (4.2)	-	27.6 (6.9)	24.6
2002	ECT	38 (9.92)	-	26 (10.63)	31.6
	p-value	NS	NS	NS	-
O'Connor et al	rTMS	-	-	-	
2003	ECT	-	-	-	
	p-value				
Schulze-R et al	rTMS	-	-	-	
2005	ECT	-	-	-	
	p-value				

ECT: electroconvulsive therapy; NS: not significant; rTMS: repetitive transcranial magnetic stimulation.

Global assessment of function scale scores

The global assessment of function (GAF) scale is used by clinicians to rate the social, occupational and psychological functioning of adults. Study outcomes are shown below.

At baseline (Figure 8), GAF scores significantly favoured patients in the rTMS treatment group (p=0.007). At the end of the treatment (four weeks, Figure 9), GAF scores favoured ECT, although this difference was not significant (p=0.44). (The GAF scale is described in Table 43, Appendix E).

Table 24 Global assessment of function scores

Study		Baseline Mean (SD)	Week 2 Mean (SD)	End of treatment Mean (SD)	Effect size (% improvement)	Follow-up Mean (SD) [time]
Pridmore et al	rTMS	-	-	-	-	-
2000	ECT	-	-	-	-	-
	p-value					
Grunhaus et al	rTMS	34.1 (11.7)	44.5 (14.7)	51.0 (18.2)	12.7	
2000	ECT	31.0 (8.5)	46.8 (17.2)	61.5 (21.5)	24.0	
	p-value	NS	NS	NS	-	
Dannon et al 2002	rTMS	NR	-	72.5 (9.4)	NA	79.8 (12.9) [3 month]; 77.8 (17.1) [6 month]
	ECT	NR	-	71.8(10.4)	NA	75.5 (13.8) [3month]; 72.8 (11.9) [6 month]
	p-value			NS	-	NS at follow-up
Grunhaus et al	rTMS	48.9 (10.8)	58.3 (17.1)	62.5 (18.8)	21.8	-
2003	ECT	39.8 (9.3)	55.0 (12.4)	60.6 (13.5)	34.3	-
	p-value	0.007	NS	NS	-	
Janicak et al	rTMS	-	-	-	-	-
2002	ECT	-	-	-	-	-
	p-value					
O'Connor et al	rTMS	-	-	-	-	-
2003	ECT	-	-	-	-	-
	p-value					
Schulze-R et al	rTMS	-	-	-	-	-
2005	ECT	-	-	-	-	-
	p-value					

ECT: electroconvulsive therapy; NR: not reported; NS: not significant; rTMS: repetitive transcranial magnetic stimulation.

Figure 8 Meta-analysis of global assessment of function scores at baseline

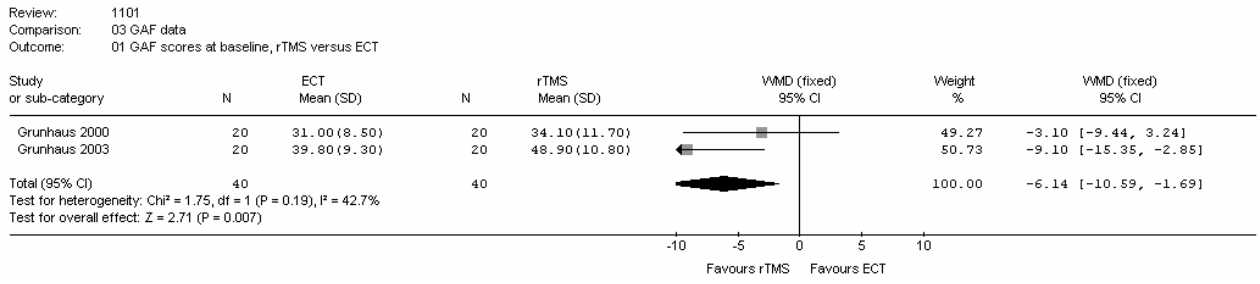
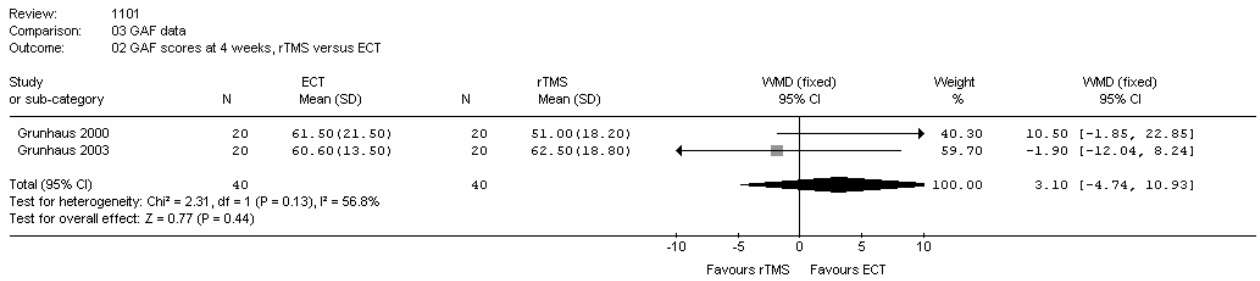


Figure 9 Meta-analysis of global assessment of function scores at four weeks



Global depression rating scores

Another widely-used measure for the severity of depression is the global depression rating (GDR) scale. GDR outcomes from the comparative studies are shown in Table 25, Figure 10 and Figure 11. For GDR scores, there was no significant difference between the rTMS group and ECT group at baseline and end of treatment (4 weeks, Figure 10 and Figure 11 respectively). However, at baseline, GDR scores slightly favour rTMS patients, while at end of treatment they favoured ECT patients.

Table 25 Global depression rating scores

Study		Baseline Mean (SD)	Week 2 Mean (SD)	End of treatment Mean (SD)	Effect size (% improvement)	Follow-up
Pridmore et al	rTMS	-	-	-		-
2000	ECT	-	-	-		-
	p-value					
Grunhaus et al	rTMS	2.4 (0.7)	1.8 (1.1)	1.3 (1.1)	45.8 (week 4)	-
2000	ECT	2.6 (0.6)	1.6 (1.1)	0.8 (1.1)	69.2 (week 4)	-
	p-value	NS	NS	NS	-	
Dannon et al	rTMS	-	-	-		-
2002	ECT	-	-	-		-
	p-value					
Grunhaus et al	rTMS	2.4 (0.5)	1.0 (1.1)	0.9 (1.1)	62.5 (week 4)	-
2003	ECT	2.5 (0.6)	1.2 (1.0)	0.85 (0.93)	66.0 (week 4)	-
	p-value	NS	NS	NS	-	
Janicak et al	rTMS	-	-	-		-
2002	ECT	-		-		-
	p-value					
O'Connor et al	rTMS	-	-	-		-
2003	ECT	-	-	-		-
	p-value					
Schulze-R et al	rTMS	-	-	-		-
2005	ECT	-	-	-		-
	p-value					

ECT: electroconvulsive therapy; NS: not significant; rTMS: repetitive transcranial magnetic stimulation.

Figure 10 Meta-analysis of global depression rating scores at baseline

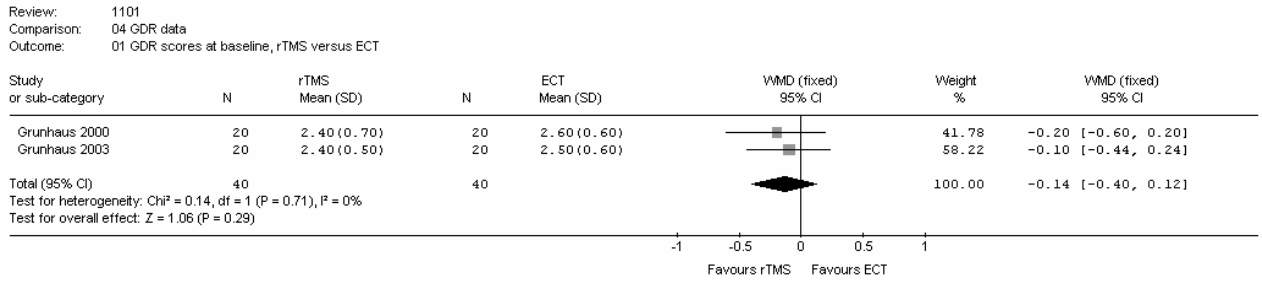
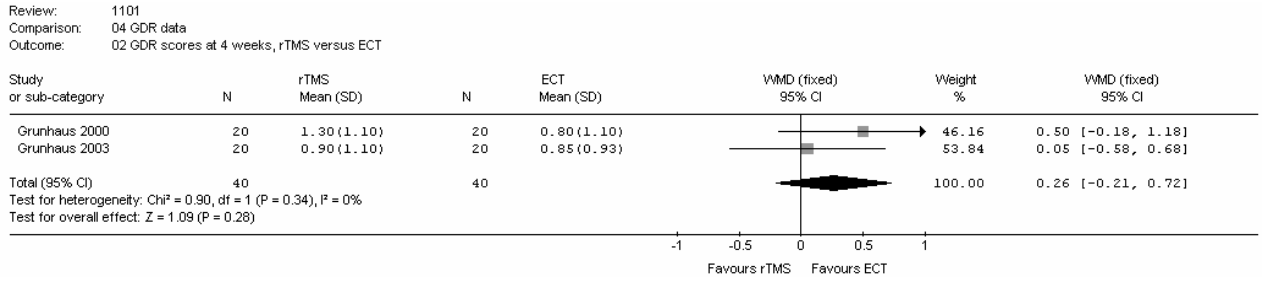


Figure 11 Meta-analysis of global depression rating scores at 4 weeks



Pittsburgh sleep quality index scores

The Pittsburgh sleep quality index (PSQI) is used to measure quality and pattern of sleep in adults. PSQI outcomes from the comparative studies, where reported, are shown below.

Table 26 Pittsburgh sleep quality index scores

Study		Baseline Mean (SD)	Week 2 Mean (SD)	End of treatment Mean (SD)	Effect size (% improvement)	Follow-up
Pridmore et al	rTMS					
2000	ECT					
	p-value					
Grunhaus et al	rTMS	11.7 (5.7)	10.1 (3.7)	10.5 (3.9)	10.3 (week 4)	-
2000	ECT	12.5 (4.4)	8.8 (4.5)	6.8 (3.5)	45.6 (week 4)	-
	p-value	NS	NS	NS	-	-
Dannon et al	rTMS					
2002	ECT					
	p-value					
Grunhaus et al	rTMS	10.4 (4.6)	9.9 (5.1)	9.4 (5.0)	9.6 (week 4)	-
2003	ECT	12.2 (4.5)	8.3 (3.9)	8.6 (4.9)	29.6 (week 4)	-
	p-value	NS	NS	NS	-	-
Janicak et al	rTMS					
2002	ECT					
O'Connor et al	rTMS					
2003	ECT					
Schulze-R et al	rTMS					
2005	ECT					

ECT: electroconvulsive therapy; NS: not significant; rTMS: repetitive transcranial magnetic stimulation.

Figure 12 Meta-analysis of Pittsburgh sleep quality index scores at baseline

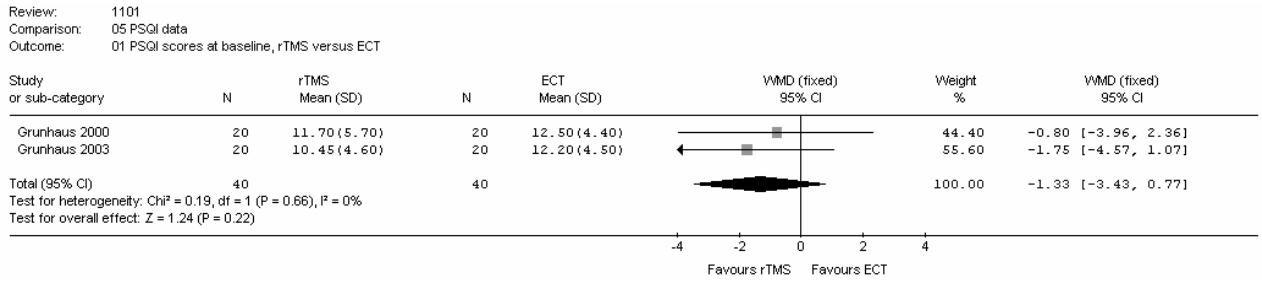
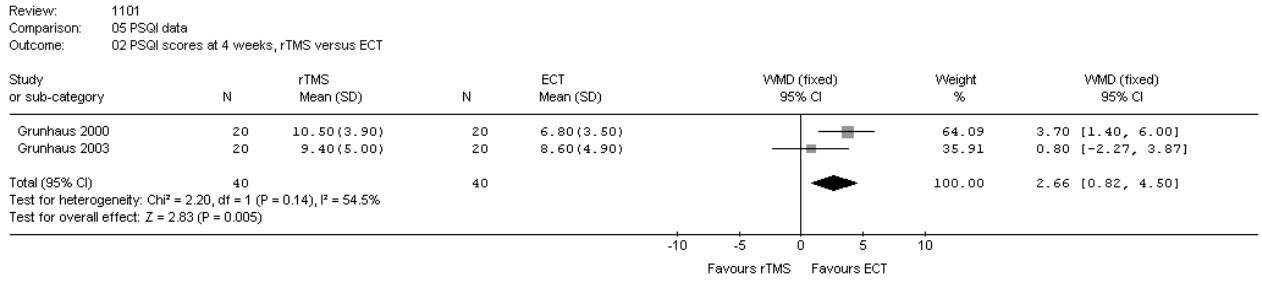


Figure 13 Meta-analysis of Pittsburgh sleep quality index scores at four weeks



Meta-analysis of the two studies that used PSQI (Table 44, Appendix E) as an outcome showed that baseline PSQI scores slightly favour patients in the rTMS group (Figure 12). At the end of treatment (four weeks, Figure 13) patients treated with ECT had significantly lower PSQI scores than patients that had been treated with rTMS (p=0.005).

Effectiveness for psychotic and non-psychotic patients

Grunhaus et al 2000 reported a sub-analysis of their data to investigate patients who suffered from psychosis, and who had depression without psychosis. This analysis appears to have been carried out 'post hoc', and was not repeated by any of the other six comparative studies.

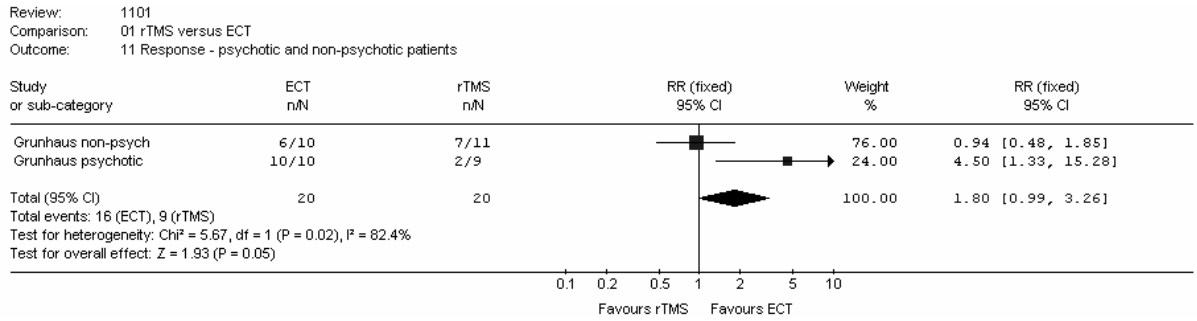
Outcomes measured as response to treatment

Table 27 Number and proportion of patients (overall, psychotic and non-psychotic) who responded to rTMS and ECT treatment (Grunhaus et al 2000)

	Responders (Y/N, %)		p-value
	rTMS	ECT	
Overall	9/11 (45%)	16/4 (80%)	P<0.05 (overall)
Psychotic	2/7 (22%)	10/0 (100%)	P<0.01
Non-psychotic	7/4 (54%)	6/4 (60%)	NS

ECT: electroconvulsive therapy; NS: not significant; rTMS: repetitive transcranial magnetic stimulation.

Figure 14 Graphical representation of the patients (psychotic and non-psychotic) who responded to rTMS and ECT treatment (Grunhaus et al 2000)



Response was defined 'a priori' as a final HDRS decreased to ≥50% from baseline and with a final GAF ≥60% (see Appendix E, Table 40 and Table 43 respectively). Response outcomes are summarised in Figure 14. ECT is significantly more effective than rTMS in the treatment of depression for patients with psychosis (p<0.01), and overall (p=0.05), but appears as effective as rTMS for the treatment of depression in patients without psychosis. This result is confirmed through the findings of response rates in studies where psychotic patients had been excluded (Table 11). In the three studies which only included non-psychotic patients (Grunhaus et al 2003; Janicak et al 2002; Schulze-Rauschenbach et al 2005), rTMS appeared approximately as effective as ECT with regard to response.

Hamilton depression scores

HDRS scores in psychotic and non-psychotic patients mirrored the final response rate shown above (see Appendix E, Table 40 for a description of the HDRS). The outcome data in Table 28 is represented in Figure 15 and Figure 16. At baseline, there were no significant differences in HDRS scores between psychotic and non-psychotic groups. At the end of treatment, outcomes for psychotic patients were significantly better following treatment with ECT compared with rTMS. For non-psychotic patients, there was no

significant difference in HDRS outcome for the groups treated with rTMS or ECT. Repetitive transcranial magnetic stimulation and ECT were equi-effective for HDRS outcome in non-psychotic patients.

Although sub-analysis of psychotic versus non-psychotic patients was only carried out in this single study, the follow-up study from this centre excluded psychotic patients (Grunhaus et al 2003). The results were that, at four weeks of treatment, rTMS and ECT were equi-effective in the treatment of non-psychotic, depressed patients (see Figure 16). In other studies which excluded psychotic patients rTMS appeared either slightly less effective than ECT (Janicak et al 2002), or slightly more effective than ECT (Schulze-Rauschenbach et al 2005), with regard to HDRS outcome.

Table 28 HDRS scores for psychotic and non-psychotic patients (Grunhaus et al 2000)

		Baseline Mean (SD)	Week 2 Mean (SD)	End of treatment Mean (SD)	% improvement (end of treatment)
Overall	rTMS	25.8 (6.1)	19.3 (8.6)	15.4 (7.5)	40.3
	ECT	28.4 (9.3)	17.6 (7.4)	11.2 (8.4)	60.6
	p-value	NS	NS	NS	
Non-psychotic	rTMS	23.5 (5.6)	15.8 (9.3)	11.0 (6.2)	53.2
	ECT	25.2 (5.3)	19.7 (7.0)	13.9 (10.3)	44.8
	p-value	NS	NS	NS	
Psychotic	rTMS	28.7 (5.6)	23.4 (5.5)	20.8 (5.0)	27.5
	ECT	31.5 (11.5)	15.5 (7.6)	8.4 (5.3)	73.3
	p-value	NS	NS	0.01	

ECT: electroconvulsive therapy; NS: not significant; rTMS: repetitive transcranial magnetic stimulation; SD: standard deviation.

Figure 15 Graphical representation of HDRS scores of psychotic and non-psychotic patients at baseline (Grunhaus et al 2000)

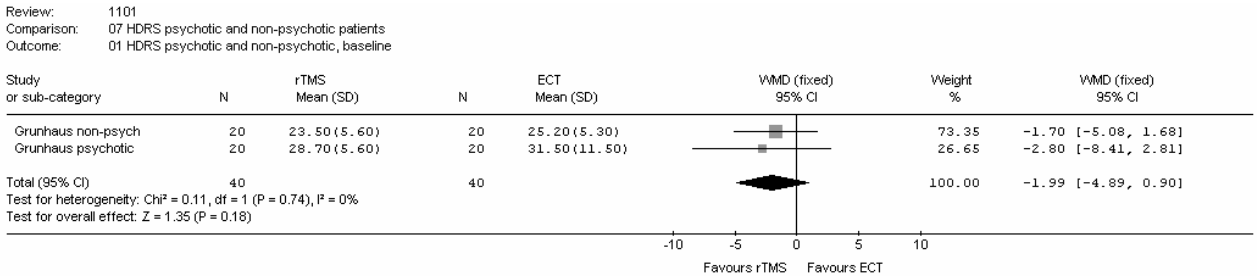
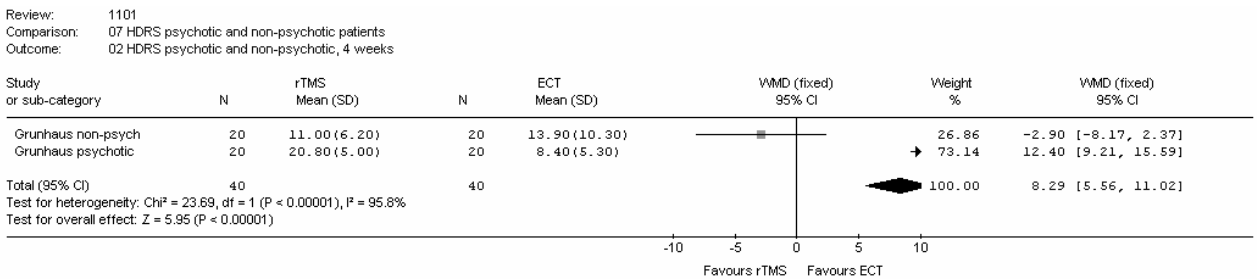


Figure 16 Graphical representation of HDRS scores of psychotic and non-psychotic patients at end of treatment (Grunhaus et al 2000)



What are the economic considerations?

An economic analysis of making rTMS available to patients might appear to be simple. For an episode of depression in a severely or moderately depressed treatment resistant (SMDTR) patient, the costs of rTMS therapy will be less than the costs of providing ECT therapy because, unlike ECT, rTMS does not require a general anaesthetic (GA). Furthermore, rTMS may allow a patient who would otherwise have been hospitalised for ECT to be treated in the community, freeing up additional bed days in public psychiatric hospitals.

However, a number of other factors complicate the analysis:

1. Repetitive transcranial magnetic stimulation is less effective than ECT. Non-responders to rTMS may go on to have ECT and therefore the cumulative costs of rTMS followed by ECT have to be considered. Some patients will not have follow-up treatment; and should also be included in the analysis.
2. Some patients using rTMS would not have had ECT. The patients who might use rTMS include those who would otherwise not have had ECT for a number of reasons despite having SMDTR.
3. Location of rTMS. Although rTMS can be delivered in the community setting, some SMDTR patients will still require hospitalisation for management of their condition.

There are two overall treatment pathways which need to be considered. The current pathway available within Medicare does not include rTMS; the second pathway is if rTMS is funded within Medicare. If rTMS is not funded, there are 7 treatment options possible for a given patient (Table 31). If rTMS is funded, more treatment alternatives (dependent on the use of ECT or rTMS and the location of treatment) become available to each group; this results in 14 possible combinations of patient and treatment options for which costs and consequences need to be modelled to compare costs in the absence of rTMS (pre-rTMS) and when rTMS is available (post-rTMS) (Table 31). The overall impact of the policy in terms of responders and additional costs to the system depend upon the extent of take up in each of the 14 groups of patients. Supply side issues will result from the introduction of a procedural fee for psychiatrists operating in their rooms and will influence the take up of rTMS in private clinics and the expected mix of patients using rTMS.

Three economic analyses were designed to help decision makers assess the trade-offs in reimbursing rTMS through the MBS. The first analysis is a cost consequence analysis that compares the financial and resource implications of the change in responder numbers according to which of the 14 possible care options were followed. Simple assumptions are made about costs and resource use, in order to focus the analysis on the complexities of referrals and utilisation. The second analysis is a whole of health system cost-effectiveness analysis (CEA) of the absence of rTMS vs when rTMS is available. It compares the net responders with the net change in financial costs, according to the sector in which the patient received rTMS and whether or not the patient would otherwise have had ECT. The third analysis is of the financial incentives for the provision of rTMS at private clinics.

Three separate sets of interim analyses informed these final three analyses: a simple financial analysis; analysis of the clinical pathway for non-responders to rTMS; and a characterisation of the costs and effects of changed policy for each of 14 pre-rTMS and post-rTMS pairs. These analyses are summarised in Table 31.

For a number of technical reasons, the economic evaluations prepared for this application use a matrix-based simulation rather than the more familiar decision analysis. The inputs of the matrix-based simulation were provided by available evidence and expert opinion, and are focused on the changes in clinician referral patterns following the availability of rTMS. For presentation purposes, the outputs from this matrix analysis are presented as two decision trees, or treatment pathways (Figure 18, Figure 19). The results that are presented in the text are the results of the matrix-based simulation not the decision tree, as the former allows greater flexibility (additional dimensions) in the specification of the problem.

All sources and assumptions have been noted in the report and in Appendix I where possible. All tables include number references (in brackets) to the detailed input table in Appendix J. Only key assumptions are contained within this summary.

Figure 17 Chart of economic analyses

Simple financial analysis			
1	Costs of a course of rTMS vs costs of a course of ECT What are the costs of a course of rTMS compared to ECT?	→	A simple costing of each of the therapy courses includes only the variable (per course) costs. The simple financial cost to the health system of rTMS in the community setting are $1,595 compared to $11,800 for ECT while admitted in a hospital (Table 29)
The clinical pathway			
2	The full clinical pathway What happens to non-responders to rTMS? Do they have ECT?	→	A published economic evaluation includes the costs of follow-up ECT for all patients who are non-responders to rTMS. Using Australian costs and estimate of current ECT use, assuming all ECT is in hospital and rTMS is in private clinics, the savings are $20M pa and 1,133 additional responders (Table 30)
3	Response over full pathway What is the response rate for those non-responders to rTMS who then have ECT?	→	The effect of ECT post failed rTMS is adjusted to take into account the overall probability of response to consecutive treatments. The response rate to ECT alone (62%), rTMS is 47.5% and ECT if failed previous rTMS is 41%. Overall response to therapy is 62%, provided all non-responders have ECT (Figure 19)
Characterising the complexities of patient treatment options			
4	Patient characteristics Will patients who would otherwise have had ECT be the only users of rTMS?	→	Patients who could have rTMS can be in one of seven groups of patients defined by their treatment (ECT or no ECT), their sector (private or public) their hospital admission status (admitted, outpatient or community) (Figure 18)
5	Effect The effect of rTMS compared to usual care will depend upon the clinical pathway without (pre) and with (post) rTMS available.	→	There are four different combinations of pre and post clinical pathways, each with a different incremental effect (pre, post): (ECT, ECT), (No ECT, rTMS), (ECT, rTMS and ECT for non-responder), (ECT, rTMS and no ECT for non-responder). The question of whether patients will have a therapy that is less effective that the alternative is considered (Figure 19 and Table 31)
6	Cost The cost compared to usual care will depend upon site and treatment type, pre and post	→	There are 11 site sector combinations and 14 different pairs of pre post costs. The incremental resource use and costs to MBS, PHI and hospitals was estimated for each combination. The financial cost of each 11 site sectors varies from $344 to $9,002 (Table 32)
The three economic analyses			
7	Analysis 1: Cost and consequences What are the costs and consequences for each pair of pre-post reimbursement care?	→	The complexity of the consequences of reimbursement of rTMS are simulated in a matrix based model then synthesised in the more familiar format of two decision trees, one with, and one without rTMS available. The costs and consequences for each pair of pre post are estimated (Figure 19, Table 33)
8	Analysis 2: Cost-effectiveness of policy of reimbursement What is the combined effect and cost of the policy across all patient groups?	→	The overall value for money of a policy of reimbursing rTMS through the MBS requires assumptions to be made about the relative uptake of rTMS for each of the potential groups of patients. The incremental cost-effectiveness (ICER) for each group of patients is combined to provide estimates of the overall effect of the policy (Table 34)
9	Analysis 3: Supply side and financial incentives The uptake of rTMS, the mix of patients who will have rTMS and the overall ICER will be influenced by the financial incentive to provide rTMS.	→	The value for money of the overall policy is critically determined by the proportion of patients in each of the groups who take up rTMS, in turn dependant on the changed financial incentives for specialists outside hospitals and thus the MBS fee. Furthermore, patients who would otherwise have seen psychiatrists may be displaced if community clinics are operating at close to full capacity (Table 35, Table 36, Table 37, Table 38, Table 39)

ECT: electroconvulsive therapy, ICER: incremental cost effectiveness, MBS: Medicare benefits schedule, PHI: private health insurers, rTMS: repetitive transcranial magnetic stimulation

Preliminary financial analysis

One study was identified which investigated the cost-effectiveness of rTMS versus ECT for severe depression in the context of the United States of America (Kozel et al 2004). Three different treatment strategies were modelled using a simple decision tree analysis: ECT alone, rTMS alone, and rTMS followed by ECT for non-responders. Rates of response were taken from a single trial (Grunhaus et al 2000), even though numerous other comparative studies were available at the time of publication (see Table 9 and Table 10). The rate of acute response to rTMS was higher than that to ECT (0.64 versus 0.60). In addition, the authors made the assumption that the rate of response to ECT after failure of rTMS was the same as the rate of response to ECT in patients who had not had rTMS. Although published data on this is extremely limited, the estimation of response rate may be overly generous. Treatment costs were estimated over one year, and included travel costs to the patient and companion, where necessary. Overall, rTMS was shown to provide improved outcomes at less cost, in terms of cost per intervention, overall costs, QALYs and cost-utility ratio.

The analysis of Kozel et al (2004) was repeated using data calculated from the results of this report, and for the Australian context (Table 29). If rTMS is assumed to be provided in the community in a private clinic and all patients who have rTMS are assumed to otherwise have ECT, then the difference in the costs of providing rTMS and ECT will be significant. A course of ECT is expected to involve 10 sessions while rTMS will involve 12. Repetitive transcranial magnetic stimulation will involve a higher MBS fee per session but not require a general anaesthetic, certain tests and a hospital stay. This simple analysis suggests that at $1,595, rTMS costs significantly less than ECT to provide under these assumptions (based on the analysis of Kozel et al 2004) (Table 29).

Table 29 Financial costs of ECT in hospital vs rTMS in community (simple); duplication of published economic evaluation

ESTIMATES	rTMS	ECT
MBS rebate		
Per treatment	$128	$156
Psychiatrist	$128	$62
Anaesthetist	$0	$94
Number of sessions	12	10
Tests	$0	$47
Per initial consultation	$65	$65
Per course	$1,595	$1,675
Hospital cost (prelim estimate)	$0	$10,125
Per day	$0	$506
Days	0	20
Total per course	$1,595	$11,800

ECT: electroconvulsive therapy, MBS: Medicare benefits schedule, rTMS: repetitive transcranial magnetic stimulation

The clinical pathway

Data from the current report indicates that the response rate to rTMS is 48 per cent whereas the response rate to ECT is 62 per cent. Despite the lower response rate, it is expected that some patients will choose to have rTMS rather than ECT. Non responders

to rTMS could have ECT as follow-up, complicating the simple financial analysis presented in Table 29.

The full clinical pathway

The single published economic analysis, Kozel et al (2004), used a decision analytic model to estimate the additional cost and effect of providing rTMS to patients at a day clinic with ECT for non-responders to rTMS, compared to ECT alone. Treatment was also provided in the maintenance period. The study found that providing rTMS first line led to a significant additional response that justified the additional costs, ie it was cost-effective. A simplified version of the Kozel decision analysis was performed for this evaluation. It assumed that all the estimated 6,212 Australian patients who had ECT in 2005 had it as a private multi-day hospital admission and all of these patients instead had rTMS in the community sector as private patients. Maintenance rTMS was not considered. The simple analysis suggests that there are substantial savings possible to the hospital sector and that the additional cost to the MBS would be at a rate of $4,336 per additional responder (Table 30).

Table 30 Simple duplication of published study using Australian data: policy options and results

rTMS plus ECT vs ECT only	
Additional responders (1)	1,133
Additional cost to MBS (2) ($)	4,913,316
Cost to MBS per additional responder (3) ($)	4,336
Savings to hospitals (4) ($)	25,276,829
Savings total ($)	20,363,512

ECT: electroconvulsive therapy, MBS: Medicare benefits schedule, rTMS: repetitive transcranial magnetic stimulation

Response over full pathway

This duplication of the published analysis revealed the two most critical and questionable assumptions of the Kozel analysis: 1) all patients who are non-responders to rTMS have follow up ECT; and 2) the response rate to follow up ECT is the same as that which would have been experienced had these non-responders to rTMS had ECT only. In simple terms the additional responders identified by Kozel only occur if the effect of introducing rTMS is to provide patients with 'two bites of the cherry' – that is the cumulative response rate for the cohort started on rTMS is $R(rTMS) + (1-R(rTMS))xR(ECT)$, where R(x) is response rate for technology x. This assumption is not supported by the evidence. A more conservative approach, and that adopted in this evaluation, is to assume that the response to ECT alone represents a ceiling for the overall response rate for the cohort started on rTMS. Furthermore, if some non-responders choose to not have ECT as second line, then responders are foregone. Importantly, these assumptions were not tested in the sensitivity analysis of Kozel 2004. [4]

[4] The paper includes the following disclosure: 'Drs George and Kozel hold several TMS related patents or invention disclosures. These are not in the area of TMS therapeutics, but rather are for new TMS machine designs as well as combining TMS with magnetic resonance imaging'.

The analyses presented for this application take a conservative approach to the response to rTMS followed by ECT for non-responders: response to rTMS (48%); response to ECT for no previous rTMS (62%); response to ECT for non-responders to rTMS (32%); and response by 100 patients to rTMS followed by ECT for non-responders (62%). The last of these estimates is 76.5 per cent under the approach used in the published study; that is, the number of responders will increase by 27 per cent if rTMS is provided in addition to ECT, despite the lower response rate for rTMS.

Patient treatment options

The availability of rTMS will significantly change the referral options (site, sector and type of therapy) for the estimated 200,000 SMDTR Australians. There are seven possible combinations of therapy, site and sector possible for SMDTR patients when ECT is the only clinical alternative to pharmaco-therapy for SMDTR patients (Table 31). If rTMS were available, there would be an additional 14 such options, including the variations in options for ECT for non-responders to rTMS. Each of these options has different combinations of cost and effect over 6 months for a SMDTR patient.

The additional options will influence the economic analyses in two ways:

1. Comparison of the health system with and without rTMS requires that 14 separate pairs of changed with and without rTMS care pathways are analysed (14 ICERs), compared to only one or two pairs in typical Health Technology Assessments (HTAs) (Table 33);

2. The financial and health implications for the population of making rTMS available are dependant upon the number and mix of patients in each of 21 (14 changed and 7 not changed) pre-post care combinations. The overall value for money of the rTMS from a health system perspective is dependent upon the relative number of patients in each of these groups, whereas for many health technologies (HTs) only total expenditure, not value for money, is dependant upon patient numbers (Table 34).

Three intermediate steps are needed before an analysis of the costs and consequences and cost-effectiveness are performed. These steps (and the section they are described in) are:

1. Characterise the pre-rTMS and post-rTMS patient groups ('Patient characteristics').

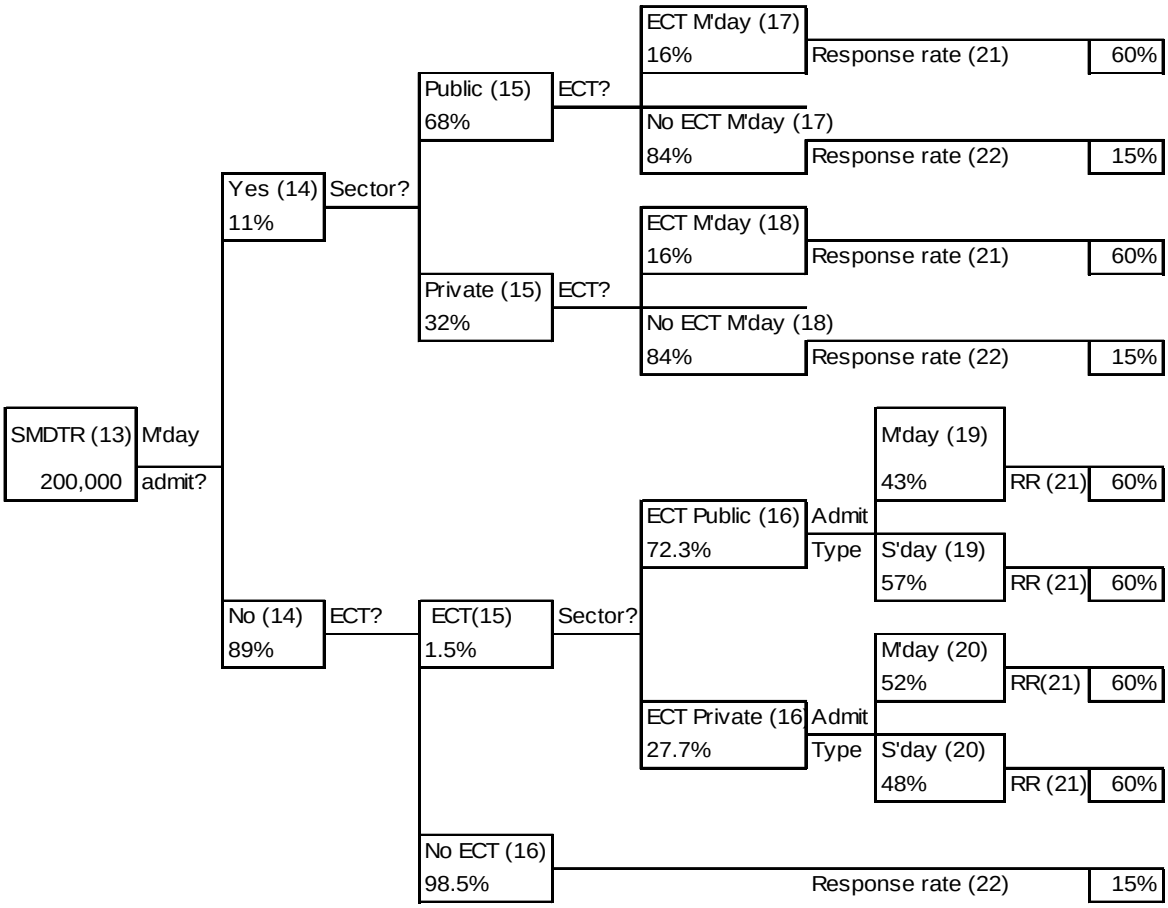
2. Quantify the effect of changed treatment pathways for each of the pre-post pairs ('Incremental effect').

3. Quantify the resource use and costs associated with each of these patient groups ('Costs and resources')

Patient characteristics

Currently, there are two sectors (public or private), three settings (multi-day admission, same day admission, community clinic) and two therapies (ECT or no ECT – each with or without pharmacotherapy) relevant to patients. This results in seven possible combinations of site, sector and therapy. These are set out in the decision tree that illustrates care without rTMS (Figure 18).

Figure 18 Treatment pathways without rTMS



ECT: electroconvulsive therapy, M'day: multiday, S'day: same day, SMDTR: severely or moderately depressed treatment resistant

This decision tree illustrates an atypical feature of the economics of rTMS and the evaluation. On the first branch (people with SMDTR who have a multiday admission for depression) the decision to admit and the decision regarding sector of admission precedes the decision to provide ECT. In contrast, on the second branch (people with SMDTR who are not admitted for depression alone) the decision to not admit is followed by a decision to provide ECT, a decision regarding the sector of ECT (public or private) and then the decision regarding type of admission (same day or multiday). In the context of this application, it is conceptually and technically useful to treat patients who have ECT coming from these two pathways because only patients who have ECT but would otherwise not have been admitted (the second branch) have the potential to have their treatment in the community setting if they have rTMS. In contrast, patients who have to be admitted regardless of whether they have ECT (the first branch) would have rTMS as an admitted patient not as a non-admitted patient.

While there are nine groups of patients represented in this tree, the remainder of the tables combine the groups who have multiday ECT regardless of whether they would otherwise have an admission, but separates them by sector. The analyses, however, maintained this separation. Table 33 presents the seven groups of patients in the absence of rTMS. When rTMS is introduced, an additional 12 possible paths to response or no response at six months are possible, including whether patients have rTMS and whether and where they have follow-up ECT. These are represented in the second decision tree that also synthesises the effect of the assumptions that populated the underlying analyses (Figure 19).

The complex paths and changes to paths are summarised in the first and second columns in Table 31 as pairs of pre-rTMS (absence of rTMS) and post-rTMS (rTMS available).

Table 31 Number of patients in each pair of with and without rTMS treatment pathways

Care in absence of rTMS	Care when rTMS available	Scenario for change	Number in each group	As %of original group (rounding)	Responders at 3 months		Follow up ECT for rTMS non-responders
					No rTMS available	rTMS available	
Public, Multi-day, ECT	Public, Multi-day, ECT (38)	No change	1,434	44%	889	889	0
	Public, Multi-day, rTMS (38)	1	1,229	38%	762	676	320
	Public, OPClinic, rTMS (38)	2	512	16%	318	282	133
	Private, clinic, rTMS (38)	3	102	3%	64	56	27
Public, Same-day, ECT	Public, Same-day, ECT (38)	No change	11	1%	7	7	0
	Public, OPClinic, rTMS (38)	4	821	77%	509	452	213
	Private, clinic, rTMS (38)	5	241	23%	150	133	63
Private, Multi-day, ECT	Private, Multi-day, ECT (38)	No change	662	44%	410	318	0
	Private, Multi-day, rTMS (38)	6	662	44%	410	364	172
	Public, OPClinic,rTMS (38)	7	19	1%	12	10	5
	Private, clinic, rTMS (38)	8	170	11%	106	94	44
Private, Same-day, ECT	Public, Same-day, ECT (38)	No change	3	1%	1	1	0
	Public, OPClinic, rTMS (38)	9	31	9%	5	17	8
	Private, clinic, rTMS (38)	10	314	90%	47	172	82
Public, Multi-day, no ECT	Public, Multi-day, no ECT or rTMS (38)	No change	6,556	50%	983	983	0
	Public, Multi-day, rTMS (38)	11	6,556	50%	983	3,147	0
Private, Multi-day, no ECT	Private, Multi-day, no ECT or rTMS (38)	No change	3,025	50%	454	454	0
	Private, Multi-day, rTMS (38)	12	3,025	50%	454	1,452	0
Private, Community, no ECT	Public, community, no ECT or rTMS (38)	No change	165,894	95%	24,884	24,884	0
	Public, OPClinic, rTMS (38)	13	873	1%	131	419	0
	Private, clinic, rTMS (38)	14	7,858	5%	1,179	3,772	0

ECT: electroconvulsive therapy, OPClinic: out patient clinic, rTMS: repetitive transcranial magnetic stimulation

Effect

The effect of pre-rTMS and post-rTMS care are summarised in Table 31. For example, a patient might otherwise have been hospitalised in a public hospital with a multiday admission and had ECT (column one, row one). When rTMS becomes available they might not change their care, they might have rTMS but remain in hospital because of the severity of their depression (scenario 2), have gone to an outpatient clinic and had rTMS (scenario 3) or had rTMS in a private setting (scenario 4). For the non responders to rTMS, some may go on to have follow-up ECT. The assumptions that were used to derive the results presented in Table 31 are contained in Appendix I. The number of responders for each group with and without rTMS, including the effect of follow-up ECT for non-responders where relevant, are presented in columns six and seven.

Cost and resource use

The number of patients in each group was applied to an estimate of the resource, treatment, activity and financial increments (changes) expected for each pre–post pathway combination. These include follow-up ECT where this occurs.

The estimates of hospital costs were not straightforward as there is a separate DRG for same-day ECT (U60Z), but not for multi-day admissions that include ECT. These are included in the DRGs for Major Affective Disorders (AR-DRG 63A (>69) and 63B (<70)). We used estimates of: the number of patients who are admitted for depression who have ECT; the additional costs of ECT; and the number of separations and bed days for AR-DRG 63A and 63B. Using these estimates we derived a cost per average admission for affective disorders, with and without ECT for the public sector. We assumed there was no difference in the average bed days for patients with and without ECT. For reasons detailed in Appendix I, we assumed that the resources used in the public sector (tests and hours), and average bed days would be the same as those in the private sector. We then assumed that the total financial costs of admissions for affective disorders, with and without ECT, would be the same in each sector as there was no evidence that this would not be the case.[5]

For the estimate of 6 months of costs of care, we included the costs of MBS consultations post discharge and, for patients in private hospitals, consultations that occurred while admitted. In the case of the cost to the state health system, we assumed the hospital cost presented in the cost weight study was the cost borne by the State.

We assumed the same total financial cost to the public sector would be borne by the funders of private hospital activity: private health insurer (PHI) and the MBS. We derived

[5] Cost data on private hospitals is not available for the previous two years. There are no separate estimates of the costs of these admissions where the patient has ECT compared to those that do not. The number of public and private hospitals that provide data for same day admissions for ECT is small and variations in year to year and sectors may be the result of sampling limitations. For these reasons we took a conservative approach and assumed that the same resources are used for these admissions when no ECT occurs, in the public and private sectors. We assumed that the additional resources required for ECT are the same in both sectors. We assumed that the financial costs of these admissions are the same in both sectors. We assumed that when rTMS is made available that the additional resource use (relative to an admission with no ECT) is the same in both sectors. However, because there are additional financial costs to the MBS to finance an hour of psychiatrist's time if they are providing ECT compared to rTMS (the surplus of rTMS over ECT), there is an additional financial cost in the private sector and this is borne by the MBS.

the share of financial cost borne by the PHIs as the total expected financial cost less the expected MBS rebate.[5] There is a possibility that there will be no change in the average financial costs of AR-DRG 63A and 63B admissions if rTMS is included. This is because the rTMS procedures may be balanced by the reduction in the number of ECT procedures. Patients are assumed to have 10 treatments per course of ECT and 12 for rTMS. If a patient has ECT following non-response to rTMS while admitted as a multi-day patient, they are assumed to have a second admission. If a patient who otherwise would have ECT has rTMS in the community sector has follow-up ECT for non-response, they will have follow-up ECT in the original setting.

Table 32 Assumed financial cost to funders for hospital activity and clinics (financial costs over 6 months per patient, by funder, including hospital discharge activity)

Pathway	MBS rebate ($)	State ($)	PHI ($)	Total ($)
Public				
Multi-day admission with ECT	172	8,830	-	9,002
Same-day admission with ECT	172	5,810	-	5,982
Multi-day admission, no ECT	172	7,602	-	7,774
Multi-day admission, with rTMS	172	7,842	-	8,014
Outpatient clinic rTMS	172	1,800	-	1,972
Private				
Multi-day admission with ECT	1,684	-	7,319	9,002
Same-day admission with ECT	1,684	-	4,298	5,982
Multi-day admission, no ECT	756	-	7,018	7,774
Multi-day admission, with rTMS	1,579	-	7,225	8,804
Clinic, community, no ECT	344	-	-	344
Clinic, community, rTMS	1,579	-	-	1,579

ECT: electroconvulsive therapy, MBS: Medicare benefits schedule, PHI: private health insurers, rTMS: repetitive transcranial magnetic stimulation

The three economic analyses

Analysis 1: Cost and consequences

The costs and consequences for each of these pre-post combinations are estimated and presented in Table 33. The ICER was calculated only for treatment pathways for which there was an improved response compared to the pathway that would otherwise have occurred. The analysis assumes that the demand generated by the changed referral patterns is completely met by providers and met within existing capacity. This assumption is explored further in the supply side analysis. As is often the case within the public hospital sector, freed bed days may be a more realistic indicator of the consequences than financial savings. In a state of the world where the demand for public sector psychiatric

beds is likely to be greater than the supply, freed bed days represent a significant benefit and are unlikely to be appropriated as financial savings.

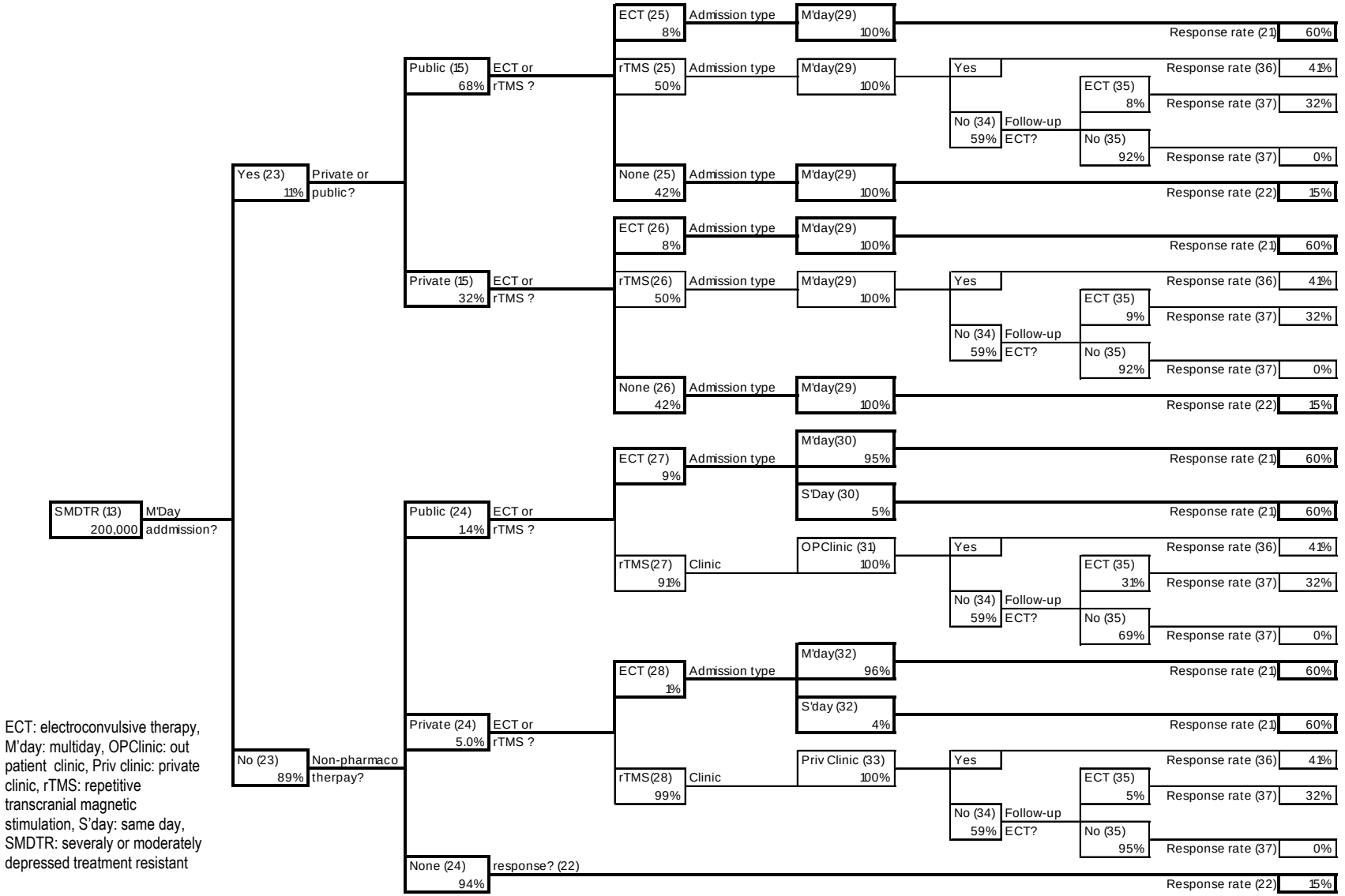
The central simulation of the cost consequence was the change in site, sector and therapy for patients. The results of the analysis of costs and effect associated with each of the treatment pathways (previous section) could then be combined with the predicted changes in pathways to estimate the costs and consequences of rTMS. The results of the simulation of existing care and care when rTMS is available and reimbursed by the MBS were represented as two decision trees, Figure 18 and Figure 19. The probabilities used at many of these nodes are not derived from a single estimate but instead a function of multiple inputs into the matrix-based simulation (Appendix I and J).

The changes in demand for rTMS were estimated using expert opinion on changes in referral patterns by psychiatrists, simulated in the matrix-based model and then represented as percentages in decision nodes in the decision tree. (The assumptions for the referrals are in Appendix I). The matrix-based method also allows patients who are non-responders to rTMS to be assigned ECT at the site and sector they would otherwise have had ECT, including no follow-up ECT for those who would otherwise not have ECT.

Each of the 14 pre-post pairs of treatment pathways for patients whose treatment changes when rTMS is available was included in the matrix analysis and the output in terms of number of patients expected to be in each treatment pathway is presented in Table 31. For example, 38 per cent (1,229) of all patients who would otherwise have had ECT as a multi-day patient in the public sector will have rTMS as a multi-day patient in the public sector, and if they fail rTMS and choose to have ECT follow-up, will have this as an multi-day patient in the public sector.

Duration of response is three months regardless of whether the patient had ECT, rTMS, pharmaco-therapy or no therapy, the response rates for which are 62 per cent, 48 per cent and 15 per cent respectively. To simplify the analysis, a 6 month time period was used. If a patient responded, this response was assumed to occur at the end of month three. Costs were estimated for 6 months by clinical pathway (See Table 32). Visits to psychiatrists were included over the 6 month period for patients in the community and discharged from hospital. This ensured that additional consultations were not over estimated: if a patient who would otherwise have been in the community had 6 consultations in those 6 months, then it would be assumed that these 6 consultations would be substituted by the 12 rTMS procedures plus initial and follow-up monthly consultations. Costs of pharmaco-therapy were not included as it is likely that patients will continue their current use (or non-use) of pharmaco-therapy regardless of whether they respond to rTMS or ECT.

Figure 19 Decision tree representing care when rTMS is available



ECT: electroconvulsive therapy, M'day: multiday, OPClinic: out patient clinic, Priv clinic: private clinic, rTMS: repetitive transcranial magnetic stimulation, S'day: same day, SMDTR: severaly or moderately depressed treatment resistant

Table 33 Cost consequence analysis of each pair of changed treatment pathways

Care in absence of rTMS	If care changes when rTMS available, what is change?(type of follow-up ECT for non-responders to rTMS)	Actual number in each cohort	Change in responders (3)	Change in Procedures		Change in Encounters					Change in resources		Change in Financing ($Million)				ICER
				ECT	rTMS	Seps Multi-day (5)	Bed days (5)	Same-day (5)	OPClinics (6)	MBS consults ex Priv hosp. (7)	Health provider hours (8)	Tests (9)	MBS (10)	State (11)	Private HI (12)	Total	Cost per additional responder
Public multi-day ECT	1. Public, multi-day, rTMS	1,229	-86	-9,096	14,751	320	4,800	0	0	959	-4,696	-1,819	0.00	1.61	0.00	1.61	n/a
	2. Public, OPClinic, rTMS (Public multi-day ECT)	512	-36	-3,790	6,146	-379	-5,692	0	6,146	0	-1,957	-758	0.00	-2.43	0.00	-2.43	n/a
	3. Prviate, clinic, rTMS (Public Multi-day ECT)	102	-7	-758	1,229	-76	-1,138	0	0	1,229	-391	-152	0.15	-0.67	0.00	-0.52	n/a
Public same-day ECT	1. Public, OPClinic, rTMS (Public same-day ECT)	821	-57	-6,075	9,851	0	0	-6,075	9,851	0	-3,136	-1,215	0.00	-2.05	0.00	-2.05	n/a
	2. Prviate, clinic, rTMS (Public Same-day ECT)	241	-17	-1,787	2,897	0	0	-1,787	0	2,897	-922	-357	0.35	-1.04	0.00	-0.69	n/a
Private multi-day ECT	1. Private, multi-day, rTMS	662	-46	-4,897	7,941	172	2,584	0	0	516	-2,528	-979	0.22	0.00	1.20	1.42	n/a
	2. Public, OPClinic, rTMS (Private multi-day ECT)	19	-1	-140	227	-14	-210	0	227	0	-72	-28	-0.02	0.03	-0.10	-0.09	n/a
	3. Private, clinic, rTMS (Private multi-day ECT)	170	-12	-1,259	2,042	-126	-1,891	0	0	2,042	-650	-252	0.057	0.00	-0.92	-0.87	n/a
Private same-day ECT	1. Public, OPClinic, rTMS (Private same-day ECT)	31	-2	-232	376	0	0	-232	376	0	-120	-46	-0.03	0.06	-0.10	-0.08	n/a
	2. Private, clinic, rTMS (Private same-day ECT)	314	-22	-2,320	3,763	0	0	-2,320	0	3,763	-1,198	-464	0.10	0.00	-1.00	-0.90	n/a
Public multi-day no ECT	1. Public, multi-day, rTMS	6,556	2,163	0	78,672	0	0	0	0	0	22,946	0	0.00	1.57	0.00	1.57	727
Private multi-day no ECT	1. Private, multi-day, rTMS	3,025	998	0	36,302	0	0	0	0	0	10,588	0	2.49	0.00	0.63	3.12	3,122
Private community no ECT	1. Public, OPClinic, rTMS (no ECT)	873	288	0	10,478	0	0	0	10,478	-2,619	5,675	0	-0.15	1.57	0.00	1.42	4,934
	2. Private, clinic, rTMS (no ECT)	7,858	2,593	0	94,298	0	0	0	0	70,723	51,078	0	9.71	0.00	0.00	9.71	3,744

ECT: electroconvulsive therapy, ICER: incremental cost effectiveness, MBS: Medicare benefits schedule, OP Clinic: out patient clinic, Priv hosp: private hospital, Private HI: private health insurers, rTMS: repetitive transcranial magnetic stimulation

Analysis 2: Cost effectiveness of policy of reimbursement

The results of the cost consequence analysis was then used to estimate the financial implications for the Australian health system and the health implications for patients (Table 34) of absence of rTMS vs rTMS available and with an MBS rebate. An important caveat to this analysis of the cost effectiveness of reimbursement is that the expected demand for rTMS is assumed to be met by the supply of rTMS. There may be capacity constraints, for example, the capacity for community psychiatrists to provide additional consultations. This issue is explored further in the third economic analysis ('Supply side issues').

The second column (Table 34) summarises the overall effect for a range of indicators. The additional cost to the MBS would be in the order of $13M, whereas the savings to the Private Health Insurers is estimated to be in the order of $0.3. The savings to the States from less admissions and bed days is offset by the costs of providing rTMS in outpatient clinics to patients who would otherwise have had same day or overnight ECT and patients who would otherwise have had no ECT and been in the community. The estimated additional 80,000 private sector consultations represent around 5 per cent of all current MBS consultations with psychiatrists. There will be an estimated 287 non-responding patients who would have responded had they had ECT rather than rTMS as first line. These are patients who would otherwise have had ECT and been responders, and would also have been responders had they chosen to have ECT as follow-up to non-response to rTMS. This compares to 6,043 patients who would not otherwise have been responders, resulting in a net increase in responders of 5,756.

Table 34 also includes a breakdown of the overall effect by groups of patients in terms of whether they would otherwise have had ECT, otherwise been hospitalised, and the sector in which they have rTMS. So for example, the total financial savings for patients who would otherwise have ECT (column 5) are estimated as $4.6, but 287 responders will be foregone. The total additional costs of patients who would otherwise have not had ECT but were hospitalised for their depression is estimated to be $4M and the cost per additional responder (three months of response) is estimated to be $1,483. The additional cost of SMDTR patients who would otherwise not have had ECT but not otherwise hospitalised is estimated to be $11.1M, after accounting for the consultations they would otherwise have had, the cost per additional responder is $3,863.

Table 34 highlights the complexities and uncertainties inherent in the uptake of this technology. Overall cost-effectiveness (the ICER of $1,952 per additional three months of response) is dependant upon the final mix of patients from each of the groups presented in the table. The savings by providing rTMS to patients who would otherwise have ECT comes at the cost of reduced responders. Of the 6,043 additional responders (patients who would otherwise not have had rTMS), 2,881 (48%) are patients who would be in the community, not otherwise considered for ECT, but have treatment resistant severe to moderate depression. This group of patients could be considered as 'item drift'. The additional MBS consultations resulting from this group is estimated to be in the order of 68,000, 85 per cent of all additional consultations. The cost per additional responder for this group is $3,863, compared to $37 per additional responder for all other patients (last column). The final column indicates the effects, excluding the group of patients who would otherwise been in the community and not had ECT, but have SMTRD. The additional costs to the health system would be expected to be small.

Univariate sensitivity analyses were performed. If the treatment response rate for rTMS were reduced from 47.5 per cent to 35 per cent, and only 25 per cent of patients who would otherwise have ECT and who were non-responders to rTMS had follow up ECT, then the foregone responders increases to 737, the overall ICER is $2,677, and the additional costs to the health care system are reduced to $7.74M. If 20 per cent instead of 5 per cent of SMTRD patients otherwise in the community used rTMS, then the overall ICER would increase to $4,037 per additional responder, the additional cost to the MBS would increase to $41M, the net additional responders increase to 11,572 and the total number of additional MBS rebatable consultations would be 284,021. This suggests that the overall financial costs and cost-effectiveness to the health sector of rTMS is largely driven by the uptake of rTMS amongst the estimated 175,000 Australians who have SMTRD but are currently in not having an admission or ECT.

Table 34 Cost effectiveness health system perspective - by sector providing rTMS therapy (CEA and cost-consequence by patient group and health system)

Unit	All Patients	Patients who would otherwise have ECT- by sector patient has rTMS			Patients who would NOT otherwise have ECT- by sector patient has rTMS							All patients ex community SMTRD- by sector patient has rTMS		
		Public	Private	Total	Otherwise hospitalised			Otherwise NOT hospitalised			Total	Public	Private	Total
					Public	Private	Total	Public	Private	Total				
Procedures														
ECT	-30,355	-19,333	-11,021	-30,355	0	0	0	0	0	0	0	-19,333	-11,021	-30,355
rTMS	268,974	31,351	17,873	49,224	78,672	36,302	114,974	10,478	94,298	104,775	219,750	110,023	54,175	164,198
Responders														
Loss	-287	-183	-104	-287	0	0	0	0	0	0	0	-183	-104	-287
Additional	6,043	0	0	0	2,163	998	3,162	288	2,593	2,881	6,043	2,163	998	3,162
Net	5,756	-183	-104	-287	2,163	998	3,162	288	2,593	2,881	6,043	1,981	894	2,875
Activity														
Multi-day seps.	-103	-135	32	-103	0	0	0	0	0	0	0	-135	32	-103
Bed days	-1,548	-2,031	483	-1,548	0	0	0	0	0	0	0	-2,031	483	-1,548
Same-day	-10,414	-6,307	-4,107	-10,414	0	0	0	0	0	0	0	-6,307	-4,107	-10,414
OPClinics	27,078	16,600	0	16,600	0	0	0	10,478	0	10,478	10,478	16,600	0	16,600
MBS Consultations	79,510	959	10,448	11,406	0	0	0	-2,619	70,723	68,104	68,104	959	10,448	11,406
Resources														
Health Professional Hours	74,618	-9,980	-5,689	-15,670	22,946	10,588	33,534	5,675	51,078	56,753	90,287	12,966	4,899	17,865
Tests	-6,071	-3,867	-2,204	-6,071	0	0	0	0	0	0	0	-3,867	-2,204	-6,071
Financing ($M)														
MBS ($M) (40)	12.87	-0.05	0.88	0.83	0.00	2.49	2.49	-0.15	9.71	9.56	12.05	-0.05	3.37	3.32
State ($M)	-1.34	-2.78	-1.71	-4.49	1.57	0.00	1.57	1.57	0.00	1.57	3.15	-1.21	-1.71	-2.91
PHI ($M)	-0.30	-0.20	-0.72	-0.92	0.00	0.63	0.63	0.00	0.00	0.00	0.63	-0.20	-0.09	-0.30
Total ($M)	11.24	-3.03	-1.55	-4.58	1.57	3.12	4.69	1.42	9.71	11.13	15.82	-1.46	1.57	0.11
ICER: $ per additional responder	1,952	n/a	n/a	n/a	n/a	n/a	1,483	n/a	n/a	3,863	2,618	n/a	n/a	37

ECT: electroconvulsive therapy, ICER: incremental cost effectiveness, MBS: Medicare benefits schedule, Multi-day seps: multi-day separations, OPClinics: outpatient clinics, PHI: private health insurers, rTMS: repetitive transcranial magnetic stimulation, SMTRD: severely or moderately depressed treatment resistant

Analysis 3: Supply side and financial incentives

The overall financial implications and effect for Australian patients are determined by the actual utilisation of rTMS, which is in turn dependent upon the combined effect of demand for rTMS by patients and referring specialists and the supply by providers in hospitals and clinics.

Typically, HTAs estimate demand for a therapy (for example, prevalence of a condition) and this is treated as the estimate of utilisation. This approach assumes all demand can be met by supply. However for a number of reasons, demand for subsidsed rTMS may be greater than supply and for this reason the expected mix of patients from each of the 14 subgroups may not represent the expected mix.

Three factors make the economics of supply of rTMS unlike typical HTAs:

1. The first atypical feature of rTMS supply is that an individual private clinic's supply of rTMS depends upon the financial incentives it faces, which in turn depends upon both the additional income (revenue less costs) per hour of rTMS vs standard consultations and the expected volume of patients (to cover the costs of equipment). Currently, there is only one MBS procedure provided by psychiatrists, viz electroconvulsive therapy. ECT requires a multi-day or same-day admission, whereas rTMS can be provided in consulting rooms. The change in financial incentives for private psychiatric clinics, which are currently providing only standard consultations, could be substantial. There may be a significant financial incentive to substitute standard consultations with procedural consultations. In addition, because the surplus[6] per consultation is volume dependant[7], there is an incentive to increase the number of rTMS procedures. The health system's supply of rTMS depends upon the number of clinics for which the required throughput can be achieved, and this may be difficult to predict. A formal analysis of the potential incentives to providers in the community is warranted and included in this evaluation.

2. The second atypical feature is that if there is a significant incentive to supply rTMS in private clinics and if private clinic psychiatric services are currently working at capacity, there is a risk that less profitable services to existing patients will be displaced. This could be in the form of longer waiting lists for patients who have schizophrenia (for example) or a provider preference for patients with depression who do not need to be bulk billed. It is useful therefore to identify the additional MBS consultations required to provide rTMS, as well as to quantify these as an additional financial cost to the MBS. It is possible that the additional consultations are supplied within current workload (no additional financial cost) and the effect is to displace other services (an opportunity cost or economic cost).

3. The third atypical factor is that unlike a surgical procedure, a psychologist or other provider including a GP could provide the service privately (without a MBS

[6] Surplus = (revenue less costs for an hour of rTMS consultations) less (revenue less costs for an hour of standard consultations).

[7] Fixed costs of equipment are apportioned across increased number of consultations.

rebate), if there is sufficient funding from private health insurers and patient fees. This possibility was not simulated as part of this evaluation. The analysis presented in this report is the additional costs to the health system of rTMS becoming available and provided by psychiatrists in consulting rooms or hospitals, not the additional cost and effect of the decision to provide a MBS rebate for rTMS.

The issue of the feasibility of supplying rTMS through private community clinics is the subject of the supply side analysis. Supply by the private hospitals will depend upon the combined effect of changed costs to the private hospitals and the revenue received from the PHIs for patients who have rTMS and the overall reduction in revenue that could occur if there are fewer admissions. This issue is not quantified for this analysis.

The analysis of the supply side issues comprised the following steps:

1. Consideration of the incentive to provide rTMS in the private community clinics

2. An economic characterisation of alternative policies (Table 35)

3. The additional profit compared to a standard community psychiatry clinic of providing only rTMS at a clinic for each possible policy for reimbursement, assuming no out of pocket fees from patients. (Table 36)

    a. The maximum number of patients who could be provided with rTMS with one FTE psychiatrist (estimated to be 197 per year)

    b. The additional revenue to the clinic under each four policies

    c. The additional costs to a clinic of providing rTMS compared to the costs of operating a standard (non procedural) clinic.

4. If a patient pays a fee above the rebate (above rebate patient fee or ARPF), at what ARPF will an rTMS only clinic be as profitable as a standard psychiatric clinic? (Table 37) This is a more realistic estimate of the capacity of an rTMS only clinic to be more profitable than a standard clinic under each of the four possible polices, as it is likely that an ARPF will be paid in many cases.

5. How much more profitable will an rTMS only clinic be at a nominal ARPF of $30 under each of the four polices? What would be the minimum number of rTMS patients per year be in order to be as profitable as a standard clinic at this nominal fee? How many clinics could provide rTMS in Australia if each were operating at exactly breakeven? (Table 38) This analysis explores the issue of the size of the market for rTMS equipment and how this is influenced by the policy for reimbursement.

6. For which policy is the cost to the MBS lowest but it is still profitable to supply rTMS to the expected number of community rTMS patients? (Table 39)

Step 1

The feasibility of supplying rTMS in private community clinics was investigated as this is where 71 per cent of the expected 148,473 MBS financed rTMS procedures (derived from Table 34) will occur and those most likely to be sensitive to the MBS fee structure for psychiatry. The proposed MBS scheduled fee of $150 would represent a substantial

increase in revenue compared to the MBS fee for an ordinary 15 to 30 minute consultation with a psychiatrist. Private psychiatric clinics do not have a procedural revenue base and the introduction of such an item will change incentive structures for clinics substantially.

Step 2

Four policy options were analysed:

1) no rebate for the consultation within which rTMS is supplied and patient pays out of pocket (Policy 1);

2) a rebate consistent with the opportunity cost of that consultation (the standard rebate for a 15 to 30 minute consultation) (Policy 2);

3) the same fee as for ECT (Policy 3);

4) the proposed scheduled fee of $150 (Policy 4).

The revenue surplus for each of these fee structures (the difference in the MBS rebate received for rTMS under that policy and the opportunity cost of the MBS rebate foregone from a standard consultation) was estimated (Table 35). An MBS rebate surplus of $62.56 will result from the proposed fee. [8]

Table 35 Surplus generated by four alterative fees for rTMS (rebates, for procedure: surplus above ordinary consultation for private clinics)

Policy	MBS rebate for procedure	MBS rebate foregone (from consultation)	Net MBS rebate
Policy 1	$0	$65	-$65
Policy 2	$65	$65	$0
Policy 3	$53	$65	-$12
Policy 4	$128	$65	$63

Step 3

The analysis presented in Table 36 examines the effect of additional costs compared to a consulting only clinic and the maximum number of patients who could be provided with rTMS in a year. The maximum number of cycles of rTMS per year (15, assuming a 3 week period over which rTMS would be provided) was estimated, and the maximum number of patients per cycle was also estimated (16, assuming 16 patients per day as a maximum). This is equivalent to 16 patients having rTMS each day for 2.5 to 3 weeks. Additionally, it was assumed that there would be no additional cost of operation, assuming that the psychiatrist or a nurse who would otherwise have been employed at the clinic that provides the therapy. The additional cost of the equipment was estimated by assuming that the psychiatrist takes out a four year loan at 10 per cent and is required to cover the repayments each year. Under this scenario, it would only be profitable to provide rTMS at maximum capacity under the proposed scheduled fee of $150. Under

[8] This analysis is intended to be indicative of the effect of changed financial incentives but further analysis would be required to identify the optimal fee, including estimates of the number of additional rTMS-related consultations to be absorbed within existing capacity.

this scenario, the additional surplus, income over and above what would be expected in a consulting only clinic and after the additional costs of the machine are considered, is $134,479 per year.

Table 36 Capacity and additional revenue and costs under policy

One private clinic site	
Maximum capacity (one FTE psychiatrist)	
Maximum cycles per year	15
Maximum patients per cycle (capacity adjusted) (41)	16
Maximum patients per year (capacity adjusted)	197
Treatments	2,359
Additional MBS rebate revenue (above consultations by clinic)	
Policy 1 (42)	-$153,213
Policy 2 (43)	$0
Policy 3 (44)	-$28,477
Policy 4 (45)	$147,598
Additional cost (46)	$13,119
Operator (annual)- costs above non procedural clinic (47)	$0
Machine (annuity payment) (48)	$13,119
Additional MBS revenue less additional service costs	
Policy 1 (42)	-$166,332
Policy 2 (43)	-$13,119
Policy 3 (44)	-$41,596
Policy 4 (45)	$134,479

FTE: full time equivalent, MBS: Medicare benefits schedule

Step 4

The previous analysis assumes that there is no patient fee above the rebate. In the analysis presented in Table 37, the breakeven above rebate patient fee was estimated for a clinic operating at maximum capacity.[9] It would be viable to provide rTMS under Policy 2 and 3 if a total of $71 or $212 were paid by the patient for the full 3 week course, above both the rebate and above what the patient would have paid as an additional fee for a standard consultation. Policy 4 would become more profitable.

[9] The additional fee is assumed to be above any above the rebate fee that would apply to standard consultations.

Table 37 Breakeven above rebate patient fee (ARPF) at maximum throughput – capacity adjusted

Policy	Breakeven ARPF (per course) (49)
Policy 1 (42)	
Per session	$71
Per course	$846
Policy 2 (43)	
Per session	$6
Per course	$67
Policy 3 (44)	
Per session	$18
Per course	$212
Policy 4 (45)	
Per session	-$57
Per course	-$684

ARPF: above rebate patient fee

Step 5

At what throughput would a clinic breakeven and how many clinics operating at breakeven could be supported? We solved for breakeven throughput for each of two possible patient fees above the rebate and above patient fee for a standard consultation, of $20 and $30 per treatment. The results are presented in Table 38. For an additional fee of $30, it would be profitable to provide rTMS under Polices 2, 3 and 4 at maximum capacity of 197 patients a year. For Policy 2, at an additional fee of $30, it would become profitable after 36 patients a year. At the 8,686 patients[10] who are expected to be referred for private clinic rTMS, 238 sites could provide rTMS at this breakeven throughput. The equivalent figures are a minimum 61 patients per clinic and a maximum 142 sites in Australia for Policy 3 and minimum 12 patients per clinic and 735 maximum sites for Policy 4.

[10] 104,229 private clinic treatments derived from Table 33, divided by 12 treatments per patient to give 8,686 patients

Table 38 Surplus and breakeven patient at a nominal above rebate patient fee (ARPF) of $30

Nominated ARPF per session (50)	$20	$30
ARPF per course of 12 treatments (51)	$240	$360
Patients- max capacity adjusted (53)	197	197
ARPF revenue (54)	$47,186	$70,779
Surplus or deficit above consultancy only clinic for a given ARPF (52)		
Policy 1 (42)	-$119,146	-$95,553
Policy 2 (43)	$34,067	$57,660
Policy 3 (44)	$5,590	$29,183
Policy 4 (45)	$181,665	$205,258
Breakeven patients, number of sites and market for machines at nominal copayment (55)		
Policy 1 (42)		
Breakeven patients (55)	n/a	n/a
Sites that could support expected patients at breakeven (56)	n/a	n/a
Market for machines (57)	n/a	n/a
Policy 2 (43)		
Breakeven patients (55)	55	36
Sites that could support expected patients at breakeven (56)	159	238
Market for machines (57)	$6,356,000	$9,534,000
Policy 3 (44)		
Breakeven patients (55)	138	61
Sites that could support expected patients at breakeven (56)	63	142
Market for machines (57)	$2,520,154	$5,698,154
Policy 4 (45)		
Breakeven patients (55)	13	12
Sites that could support expected patients at breakeven (56)	656	735
Market for machines (57)	$26,237, 568	$29,415,568

ARPF: above rebate patient fee

Step 6

Finally, the number of sites that could be supported with the expected demand for private clinic rTMS and two nominal above rebate patient fees of $20 and $30 per session were estimated (Table 39). For the expected 8,686 patients, 44 to 45 sites operating at maximum capacity could be supported. This per clinic throughput would be profitable under policies 2, 3, and 4 and would represent a market of $1.8M for rTMS machines. Under policy 4, the proposed scheduled fee of $150, there would be a surplus to the providers of in excess of $9M, if a fee of $30 above the rebate is paid by patients. The implication for cost-effectiveness of reimbursement is that if these sites are operating at full capacity, they will be more profitable (after additional costs of equipment) than a clinic that operates at full capacity with standard consultations only under rebates consistent with the previously described polices 2, 3, and 4. While policy 4 (the scheduled fee of $150) could be considered cost-effective, it would still be more profitable for a clinic to operate at the lower fees of policy 2 and 3 with only rTMS

patients compared to a clinic that is providing standard (non-procedural consultations) only. The additional profit at policy 2 is a result of the additional ARPF above what would be paid by a patient for a standard consultation and the reduced time involved in providing rTMS compared to a standard consultation. The higher the additional profit from an rTMS only clinic compared to a standard clinic the greater incentive to displace standard consultations to provide rTMS. If the current community based psychiatry clinics are operating at capacity, then the number of current patients who are displaced could be high.

Table 39 Number of sites that can be supported with expected demand for private clinic rTMS

Nominated ARPF per session (58)	$20	$30
ARPF per course (59)	$240	$360
Sites supporting expected private clinic patients, at maximum capacity (60)		
Expected patients (41)	8,686	8,686
Maximum patients per site (capacity adjusted) (41)	197	197
Sites supporting expected patients-sites operating at maximum capacity (61)	44	44
Size of market for machines in private sector at max capacity (62)	$1,767,122	$1,767,122
National surplus above consulting only clinic at max capacity (adj) and nominated ARPF and max sites (63)		
Policy 1 (42)	-$5,263,621	-$4,221,330
Policy 2 (43)	$1,505,018	$2,547,309
Policy 3 (44)	$246,972	$1,289,264
Policy 4 (45)	$8,025,592	$9,067,883

ARPF: above rebate patient fee, rTMS: repetitive transcranial magnetic stimulation

Discussion

Limits of the evidence

Although seven comparative studies were identified which investigated the treatment of severely depressed individuals with rTMS and ECT, all the studies were relatively small. The largest studies which reported treatment effects had 40 patients, and there were a total of 233 patients completing treatment in all seven studies. An eighth study comparing the effectiveness of rTMS and ECT in treating refractory depression was e-published ahead of publication in late August 2006 (Rosa et al 2006). This study was not included in the review as it was published well after the official dates of the search strategy. There were a total of 42 participants in the study. Briefly, the results were that there was no significant difference between the response rates of the rTMS group and the ECT group. In addition to this manuscript two trials will be published over the next few months which will greatly increase the evidence base for the effectiveness of rTMS in treating depression. A study based in the UK (Eranti et al 2007) compared rTMS versus ECT, and the Neuronetics international multi-centre trial which compared rTMS with sham treatment. These trials (combined) reportedly randomised approximately 300 participants. Eranti et al 2007 and Rosa et al 2006 are discussed in Appendix H.

Safety

Although comment can be made on the absolute safety of rTMS, where the total numbers of serious adverse events were relatively small there was poor comparative data on rTMS versus ECT. Only one study (Pridmore et al 2000) reported in detail the adverse events for both rTMS and ECT procedures, and this result was inconclusive. Therefore from the comparative data the overall safety profile of rTMS may not be much better than ECT, as is frequently assumed. Repetitive transcranial magnetic stimulation may, however, have improved cognitive outcomes over ECT in the treatment of major depression, although the results from different cognitive tests were variable.

Investigation of all available studies (level II, III and IV) showed that there were no specific technical specifications of the rTMS procedure which were more or less safe. Switches to a manic state during rTMS treatment were mainly seen in patients who presented with bipolar depression.

Effectiveness

Overall, rTMS appeared to slightly be less effective than ECT in the treatment of major depression, although this was not statistically significant. However, the low sample size was not sufficient to detect small differences in effectiveness. Data from a single study (Grunhaus et al 2000) suggested that rTMS may have been as effective as ECT in the treatment of depression in non-psychotic patients. It was not possible to investigate the effect of continuing anti-depressant medication on

the effectiveness of rTMS as only one of the included studies which reported full effectiveness outcomes had subjects remaining on medications; all other trials removed patients from medications prior to rTMS or ECT.

Cost-effectiveness

The costs and consequences of rTMS vary in magnitude and direction by patient (who would otherwise have ECT and/or otherwise be hospitalised), site (multi-day or same day admission, outpatient or private clinic) and sector (public or private). The overall net increase in responders and financial and resource implications depend upon the mix of patients who have rTMS. The overall effect is dependant upon the rate of uptake amongst patients with severe to moderate treatment resistant depression who would otherwise not have ECT for a range of reasons and have their care in the community at private clinics. It is unlikely that the expected freed bed days in public psychiatric hospitals will be appropriated as financial savings but instead the days have value in improved access for psychiatric patients. It is unlikely that the entire estimated additional MBS private clinic consultations will be met within capacity. This will reduce the additional cost to the MBS but may be at a cost to displaced services. A single statement on cost-effectiveness is not applicable to this decision. The decision for the reimbursement of rTMS requires that the trade-offs between additional bed days and responders, and displaced private clinic consultations and foregone responders, are addressed.

Conclusions

Repetitive transcranial magnetic stimulation appears to be a relatively safe treatment for severe, treatment–resistant depression in comparison to ECT with few major adverse events detected in total (from 128 included studies with a total of 1931 participants). There were no data for long-term or repeat use of rTMS. Overall effectiveness of rTMS versus ECT was calculated using response to treatment as the main outcome (defined as a reduction in the final Hamilton depression rating score of 50% or more from baseline). A meta-analysis of the four comparative studies gave a relative risk of 1.28 (95% CI 0.93, 1.76). Although these results slightly favour ECT, this is not a statistically significant difference (p=0.12), and the small patient numbers used (132 participants in total) do not allow the detection of small differences in effectiveness. Due to the relatively small number of comparative studies available (7), and their reasonably similar methodology, it was not possible to undertake any subgroup analyses (such as to investigate the effects of different rTMS treatments eg high or low frequency, or the effects of medications on treatment effectiveness). Study data suggests that rTMS may have improved effectiveness for patients who suffer from non-psychotic severe depression, ie rTMS and ECT are equi-effective.

The costs and consequences of rTMS treatment vary in magnitude and direction by patient (would otherwise have ECT and/or otherwise be hospitalised), site (multi-day, same-day admission and outpatient or private clinic) and sector (public and private). The additional costs per additional responder (3 months depression-free) is estimated to be $1,952. It is expected that approximately 22,000 patients with severe to moderate treatment resistant depression (SMTRD) will have rTMS annually; of these, 18,000 will not otherwise have had ECT, and of these, 9,000 will not have otherwise been hospitalised. The expected net increase in responders (5,756) and financial and resource implications (additional $12.9M to the MBS and $11.2M to health system overall) depends upon the mix of patients who have rTMS and uptake by SMTRD patients who are currently treated in the community. The expected freed same-day beds in public psychiatric hospitals or units (approximately 6,000) will be offset by the additional outpatient clinic sessions (approximately 14,000). There is a net increase in the total number of multi-day admissions (approximately 130) because only a small proportion of patients who would otherwise had ECT and a multi-day admission, are expected to have rTMS outside the hospital and hence free multi-day beds. Of patients who would otherwise have ECT and a multi-day admission, 59 per cent are expected to be non-responders to rTMS and 50 per cent of these are expected to have a follow-up admission for ECT (or a second admission if rTMS is as multi-day admission). It is unlikely that the entire estimated additional MBS rebateable private clinic consultations (80,000 or 5% of all current MBS rebateable consultations with psychiatrists) will be met within capacity. This will reduce the additional cost to the MBS but may be at a cost to displaced services.

Recommendation

MSAC recommended that on the strength of evidence pertaining to Application 1101, repetitive transcranial magnetic stimulation as a treatment for major depression, public funding should not be supported for this procedure.

- The Minister for Health and Ageing endorsed this recommendation on 4 June 2007 -

MSAC has considered the safety, effectiveness and cost-effectiveness of repetitive transcranial magnetic stimulation (rTMS) for moderate to severe refractory treatment resistant depression compared with electro convulsive therapy (ECT).

MSAC finds evidence that rTMS is safe and less invasive than ECT.

MSAC finds limited evidence that rTMS may be less effective than ECT.

The financial and resource implications will depend upon the mix of patients who have rTMS, including uptake amongst patients who would otherwise not have ECT.

At present, MSAC finds there is insufficient evidence to support public funding.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or Affiliation**
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Ms Catherine Farrell	Department of Health and Ageing representative
Dr Kwun Fong	thoracic medicine
Dr David Gillespie	gastroenterology
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology

Associate Professor Frederick Khafagi	nuclear medicine
Dr Ray Kirk	health research
Dr Ewa Piejko	general practice
Ms Sheila Rimmer	consumer health issues
Professor Ken Thomson	radiology
Dr Douglas Travis	urology
Dr Mary Turner	Australian Health Ministers' Advisory Council representative
Dr David Wood	orthopaedics

Appendix B Advisory Panel

Advisory Panel MSAC Application 1101

Repetitive transcranial magnetic stimulation as a treatment for major depression

Dr Kwun Fong (Chair) MBBS (London), FRACP, PhD Thoracic physician	Member of MSAC
Dr Mary Turner (Deputy Chair) MBBS (Adel Uni), Dip (Community Child Health), MHA, MBA, FRACP (Paediatrics), FRACMA	Member of MSAC
Dr Steven Kan MBBS (WA) General Medicine	Royal Australian College of General Practitioners nominee
Professor Philip Mitchell, MB BS (Sydney), MD (UNSW), FRANZCP, FRCPsych Psychiatry	Royal Australian and New Zealand College of Psychiatrist nominee
Ms Margaret Springgay, Master Health Care Management, Grad Dip Health Counselling	Consumers' Health Forum of Australia nominee
Professor Philip Thompson, MBBS (Adelaide), PhD (London) FRACP Neurology	Australian Association of Neurologists nominee

Appendix C Studies included in the review

Repetitive TMS versus ECT comparators; comparative studies

Dannon PN, Dolberg OT, Schreiber S, Grunhaus L. Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals-preliminary report. *Biological Psychiatry* 2002; **51**(8): 687-690.

Grunhaus L, Dannon PN, Schreiber S, Dolberg OH, Amiaz R, Ziv R, Lefkifker E. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biological Psychiatry* 2000; **47**(4): 314-324.

Grunhaus L, Schreiber S, Dolberg OT, Polak D, Dannon PN. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biological Psychiatry* 2003; **53**(4): 324-331.

Janicak PG, Dowd SM, Martis B, Alam D, Beedle D, Krasuski J, Strong MJ, Sharma R, Rosen C, Viana M. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: Preliminary results of a randomized trial. *Biological Psychiatry* 2002; **51**(8): 659-667.

O'Connor M, Brenninkmeyer C, Morgan A, Bloomingdale K, Thall M, Vasile R, Leone AP. Relative effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy on mood and memory: a neurocognitive risk-benefit analysis. *Cognitive & Behavioural Neurology* 2003; **16**(2): 118-127.

Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *International Journal of Neuropsychopharmacology* 2000; **3**(2): 129-134.

Schulze-Rauschenbach SC, Harms U, Schlaepfer TE, Maier W, Falkai P, Wagner M. Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression.[see comment]. *British Journal of Psychiatry* 2005; **186**: 410-416.

Studies which reported rTMS compared with sham treatment

The following is a list of included studies where rTMS was compared with sham treatment for the treatment of severe depression. All of the following are randomised controlled trials and were found using the search strategy cited in this Review. These studies were extracted for safety outcomes, and for effectiveness outcomes in Appendix G (rTMS versus sham studies).

Of these studies, the following report response as an outcome (usually defined as a greater, or equal to 50% reduction in baseline HDRS) - Avery 2006, Chistyakov 2005, Garcia-Toro 2001, George 2000, Herwig 2003, Holtzheimer 2004, Hoppner 2003, Januel 2006, Kauffmann 2004, Klein 1999, Loo 2003, Manes 2001, Mosimann 2004, Nahas 2001, Nahas 2003, Padberg 2002, Rumi 2005, Su 2005.

Avery DH, Claypoole K, Robinson L, Neumaier JF, Dunner DL, Scheele L, Wilson L, Roy-Byrne P. Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. *Journal of Nervous & Mental Disease* 1999; **187**(2): 114-117.

Avery DH, Holtzheimer PE, III, Fawaz W, Russo J, Neumaier J, Dunner DL, Haynor DR, Claypoole KH, Wajdik C, Roy-Byrne P. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biological Psychiatry* 2006; **59**(2): 187-194.

Berman RM, Narasimhan M, Sanacora G, Miano AP, Hoffman RE, Hu XS, Charney DS, Boutros NN. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biological Psychiatry* 2000; **47**(4): 332-337.

Boutros NN, Gueorguieva R, Hoffman RE, Oren DA, Feingold A, Berman RM. Lack of a therapeutic effect of a 2-week sub-threshold transcranial magnetic stimulation course for treatment-resistant depression. *Psychiatry Research* 2002; **113**(3): 245-254.

Chistyakov AV, Kaplan B, Rubichek O, Kreinin I, Koren D, Feinsod M, Klein E. Antidepressant effects of different schedules of repetitive transcranial magnetic stimulation vs. clomipramine in patients with major depression: Relationship to changes in cortical excitability. *International Journal of Neuropsychopharmacology* 2005; **8**(2): 223-233.

Conca A, Di Pauli J, Beraus W, Hausmann A, Peschina W, Schneider H, Konig P, Hinterhuber H. Combining high and low frequencies in rTMS antidepressive treatment: preliminary results. *Human Psychopharmacology-Clinical and Experimental* 2002; **17**(7): 353-356.

Dolberg OT, Dannon PN, Schreiber S, Grunhaus L. Transcranial magnetic stimulation in patients with bipolar depression: a double blind, controlled study. *Bipolar Disorders* 2002; **4** : Suppl-5.

Eichhammer P, Kharraz A, Wiegand R, Langguth B, Frick U, Aigner JM, Hajak G. Sleep deprivation in depression stabilizing antidepressant effects by repetitive transcranial magnetic stimulation. *Life Sciences* 2002; **70**(15): 1741-1749.

Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, de Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Archives of General Psychiatry* 2003; **60**(10): 1002-1008.

Garcia-Toro M, Pascual-Leone A, Romera M, Gonzalez A, Mico J, Ibarra O, Arnillas H, Capllonch I, Mayol A, Tormos JM. Prefrontal repetitive transcranial magnetic stimulation as add on treatment in depression. *Journal of Neurology, Neurosurgery & Psychiatry* 2001; **71**(4): 546-548.

Garcia-Toro M, Mayol A, Arnillas H, Capllonch I, Ibarra O, Crespi M, Mico J, Lafau O, Lafuente L. Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. *Journal of Affective Disorders* 2001; **64**(2-3): 271-275.

Garcia-Toro M, Salva J, Daumal J, Andres J, Romera M, Lafau O, Echevarria M, Mestre M, Bosch C, Collado C, Ibarra O, Aguirre I. High (20-Hz) and low (1-Hz) frequency transcranial magnetic stimulation as adjuvant treatment in medication-resistant depression. *Psychiatry Research: Neuroimaging* 2006; **146**(1): 53-57.

George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, Greenberg BD, Hallett M, Post RM. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial.[see comment]. *American Journal of Psychiatry* 1997; **154**(12): 1752-1756.

George MS, Nahas Z, Molloy M, Speer AM, Oliver NC, Li XB, Arana GW, Risch SC, Ballenger JC. A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biological Psychiatry* 2000; **48**(10): 962-970.

Hansen PE, Videbech P, Clemmensen K, Sturlason R, Jensen HM, Vestergaard P. Repetitive transcranial magnetic stimulation as add-on antidepressant treatment. The applicability of the method in a clinical setting. *Nordic Journal of Psychiatry* 2004; **58**(6): 455-457.

Hausmann A, Pascual-Leone A, Kemmler G, Rupp CI, Lechner-Schoner T, Kramer-Reinstadler K, Walpoth M, Mechtcheriakov S, Conca A, Weiss EM. No deterioration of cognitive performance in an aggressive unilateral and bilateral antidepressant rTMS add-on trial. *Journal of Clinical Psychiatry* 2004; **65**(6): 772-782.

Herwig U, Lampe Y, Juengling FD, Wunderlich A, Walter H, Spitzer M, Schonfeldt-Lecuona C. Add-on rTMS for treatment of depression: a pilot study using stereotaxic coil-navigation according to PET data. *Journal of Psychiatric Research* 2003; **37**(4): 267-275.

Holtzheimer III PE, Russo J, Claypoole KH, Roy-Byrne P, Avery DH. Shorter duration of depressive episode may predict response to repetitive transcranial magnetic stimulation. *Depression & Anxiety* 2004; **19**(1): 24-30.

Hoppner J, Schulz M, Irmisch G, Mau R, Schlafke D, Richter J. Antidepressant efficacy of two different rTMS procedures. High frequency over left versus low frequency over right prefrontal cortex compared with sham stimulation. *European Archives of Psychiatry & Clinical Neuroscience* 2003; **253**(2): 103-109.

Januel D, Dumortier G, Verdon C-M, Stamatiadis L, Saba G, Cabaret W, Benadhira R, Rocamora J-F, Braha S, Kalalou K, Vicaut P, Fermanian J. A double-blind sham controlled study of right prefrontal repetitive transcranial magnetic stimulation (rTMS): Therapeutic and cognitive effect in medication free unipolar depression during 4 weeks. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2006; **30**(1): 126-130.

Kauffmann CD, Cheema MA, Miller BE. Slow right prefrontal transcranial magnetic stimulation as a treatment for medication-resistant depression: a double-blind, placebo-controlled study. *Depression & Anxiety* 2004; **19**(1): 59-62.

Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, Repella JD, Danielson AL, Willis MW, Benson BE, Speer AM, Osuch E, George MS, Post RM. Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. *Biological Psychiatry* 1999; **46**(12): 1603-1613.

Klein E, Kreinin I, Chistyakov A, Koren D, Mecz L, Marmur S, Ben Shachar D, Feinsod M. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study.[see comment]. *Archives of General Psychiatry* 1999; **56**(4): 315-320.

Koerselman F, Laman DM, van Duijn H, van Duijn MA, Willems MA. A 3-month, follow-up, randomized, placebo-controlled study of repetitive transcranial magnetic stimulation in depression. *Journal of Clinical Psychiatry* 2004; **65**(10): 1323-1328.

Kolbinger HM, Hoflich G, Hufnagel A, Moller H-J, Kasper S. Transcranial magnetic stimulation (TMS) in the treatment of major depression - A pilot study. *Human Psychopharmacology* 1995; **10**(4): 305-310.

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Loo C, Sachdev P, Elsayed H, McDarmont B, Mitchell P, Wilkinson M, Parker G, Gandevia S. Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. *Biological Psychiatry* 2001; **49**(7): 615-623.

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Miniussi C, Bonato C, Bignotti S, Gazzoli A, Gennarelli M, Pasqualetti P, Tura GB, Ventriglia M, Rossini PM. Repetitive transcranial magnetic stimulation (rTMS) at high and low frequency: an efficacious therapy for major drug-resistant depression? *Clinical Neurophysiology* 2005; **116**(5): 1062-1071.

Moser DJ, Jorge RE, Manes F, Paradiso S, Benjamin ML, Robinson RG. Improved executive functioning following repetitive transcranial magnetic stimulation. *Neurology* 2002; **58**(8): 1288-1290.

Mosimann UP, Schmitt W, Greenberg BD, Kozel M, Muri RM, Berkhoff M, Hess CW, Fisch HU, Schlaepfer TE. Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. *Psychiatry Research* 2004; **126**(2): 123-133.

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Nahas Z, Teneback CC, Kozel A, Speer AM, DeBrux C, Molloy M, Stallings L, Spicer KM, Arana G, Bohning DE, Risch SC, George MS. Brain effects of TMS delivered over prefrontal cortex in depressed adults: role of stimulation frequency and coil-cortex distance. *Journal of Neuropsychiatry & Clinical Neurosciences* 2001; **13**(4): 459-470.

Nahas Z, Kozel FA, Li X, Anderson B, George MS. Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. *Bipolar Disorders* 2003; **5**(1): 40-47.

Padberg F, Zwanzger P, Thoma H, Kathmann N, Haag C, Greenberg BD, Hampel H, Moller HJ. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Research* 1999; **88**(3): 163-171.

Padberg F, Zwanzger P, Keck ME, Kathmann N, Mikhaiel P, Ella R, Rupprecht P, Thoma H, Hampel H, Toschi N, Moller HJ. Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. *Neuropsychopharmacology* 2002; **27**(4): 638-645.

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Rossini D, Magri L, Lucca A, Giordani S, Smeraldi E, Zanardi R. Does rTMS hasten the response to escitalopram, sertraline, or venlafaxine in patients with major depressive disorder? A double-blind, randomized, sham-controlled trial. *Journal of Clinical Psychiatry* 2005; **66**(12): 1569-1575.

Rossini D, Lucca A, Zanardi R, Magri L, Smeraldi E. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. *Psychiatry Research* 2005; **137**(1-2): 1-10.

Rumi DO, Gattaz WF, Rigonatti SP, Rosa MA, Fregni F, Rosa MO, Mansur C, Myczkowski ML, Moreno RA, Marcolin MA. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. *Biological Psychiatry* 2005; **57**(2): 162-166.

Su TP, Huang CC, Wei IH. Add-on rTMS for medication-resistant depression: a randomized, double-blind, sham-controlled trial in Chinese patients. *Journal of Clinical Psychiatry* 2005; **66**(7): 930-937.

Szuba MP, O'Reardon JP, Rai AS, Snyder-Kastenberg J, Amsterdam RD, Gettes DR, Wassermann EM, Evans DL. Acute mood and thyroid stimulating hormone effects of transcranial magnetic stimulation in major depression. *Biological Psychiatry* 2001; **50**: 22-27.

Other rTMS randomised controlled trials

The following RCTs were included for safety outcomes only. They did not compare rTMS with ECT. The reason for exclusion from Appendix G (rTMS versus sham studies) is given in parenthesis after each reference.

Isenberg K, Downs D, Pierce K, Svarakic D, Garcia K, Jarvis M, North C, Kormos TC. Low frequency rTMS stimulation of the right frontal cortex is as effective as high frequency rTMS stimulation of the left frontal cortex for antidepressant-free, treatment-resistant depressed patients. *Annals of Clinical Psychiatry* 2005; **17**(3): 153-159. (No sham reported).

Kirov G, Tredget J, Dunn E, Moskvina V, Beer R, Khalid N, Koerselman F. Underpowered repetitive transcranial magnetic stimulation might not be an effective antidepressant treatment. *Journal of Clinical Psychiatry* 2005; **66**(4): 543-544. (No sham reported).

Little JT, Kimbrell TA, Wassermann EM, Grafman J, Figueras S, Dunn RT, Danielson A, Repella J, Huggins T, George MS, Post RM. Cognitive effects of 1- and 20-hertz repetitive transcranial magnetic stimulation in depression: preliminary report. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology* 2000; **13**(2): 119-124. (No sham reported).

Rybak M, Bruno R, Turnier-Shea Y, Pridmore S. An attempt to increase the rate and magnitude of the antidepressant effect of transcranial magnetic stimulation (TMS). A pilot study. *German Journal of Psychiatry* 2005; **8**(4): 59-65. (Crossover study).

Shajahan PM, Glabus MF, Steele JD, Doris AB, Anderson K, Jenkins JA, Gooding PA, Ebmeier KP. Left dorso-lateral repetitive transcranial magnetic stimulation affects cortical excitability and functional connectivity, but does not impair cognition in major depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2002; **26**(5): 945-954. (No sham reported).

Speer AM, Kimbrell TA, Wassermann EM, Repella D, Willis MW, Herscovitch P, Post RM. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biological Psychiatry* 2000; **48**(12): 1133-1141. (No sham reported).

Speer AM, Repella JD, Figueras S, Demian NK, Kimbrell TA, Wasserman EM, Post RM. Lack of adverse cognitive effects of 1 Hz and 20 Hz repetitive transcranial magnetic stimulation at 100% of motor threshold over left prefrontal cortex in depression. *Journal of Ect* 2001; **17**(4): 259-263. (Depression-related outcomes not reported)

Teneback CC, Nahas Z, Speer AM, Molloy M, Stallings LE, Spicer KM, Risch SC, George MS. Changes in prefrontal cortex and paralimbic activity in depression following two weeks of daily left prefrontal TMS. *Journal of Neuropsychiatry & Clinical Neurosciences* 1999; **11**(4): 426-435. (No sham reported).

Repetitive TMS case series and case reports (level IV)

Abraham G and O'Brien S. Repetitive transcranial magnetic stimulation is useful for maintenance treatment. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie* 2002; **47**(4): 386.

Bajbouj M, Brakemeier EL, Schubert F, Lang UE, Neu P, Schindowski C, Danker-Hopfe H. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex and cortical excitability in patients with major depressive disorder. *Experimental Neurology* 2005; **196**(2): 332-338.

Boechat-Barros R and Brasil-Neto JP. Transcranial Magnetic Stimulation in depression: Results of bi-weekly treatment. *Revista Brasileira de Psiquiatria* 2004; **26**(2): 100-102.

Catafau AM, Perez V, Gironell A, Martin JC, Kulisevsky J, Estorch M, Carrio I, Alvarez E. SPECT mapping of cerebral activity changes induced by repetitive transcranial magnetic stimulation in depressed patients. A pilot study. *Psychiatry Research* 2001; **106**(3): 151-160.

Cohen CI, Amassian VE, Akande B, Maccabee PJ. The efficacy and safety of bilateral rTMS in medication-resistant depression. *Journal of Clinical Psychiatry* 2003; **64**(5): 613-614.

Conca A, Konig P, Hausmann A, Gangadhar BN. Transcranial magnetic stimulation induces 'pseudoabsence seizure'. *Acta Psychiatrica Scandinavica* 2000; **101**(3): 246-249.

Conca A, Peschina W, Konig P, Fritzsche H, Hausmann A. Effect of chronic repetitive transcranial magnetic stimulation on regional cerebral blood flow and regional cerebral glucose uptake in drug treatment-resistant depressives. A brief report. *Neuropsychobiology* 2002; **45**(1): 27-31.

Conca A, Hrubos W, Di Pauli J, Konig P, Hausmann A. ECT response after relapse during continuation repetitive transcranial magnetic stimulation. A case report. *European Psychiatry: the Journal of the Association of European Psychiatrists* 2004; **19**(2): 118-119.

Crevits L, Van den AD, Audenaert K, Goethals M, Dierick M. Effect of repetitive transcranial magnetic stimulation on saccades in depression: a pilot study. *Psychiatry Research* 2005; **135**(2): 113-119.

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Epstein CM, Figiel GS, McDonald WM, Amazon-Leece J, Figiel L. Rapid rate transcranial magnetic stimulation in young and middle-aged refractory depressed patients. *Psychiatric Annals* 1998; **28**(1): 36-39.

Eschweiler GW, Plewnia C, Batra A, Bartels M. Does clinical response to repetitive prefrontal transcranial magnetic stimulation (rTMS) predict response to electroconvulsive therapy (ECT) in cases of major depression? *Canadian Journal of Psychiatry-Revue Canadienne de Psychiatrie* 2000; **45**(9): 845-846.

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Holtzheimer P, Fawaz W, Wilson C, Avery D. Repetitive transcranial magnetic stimulation may induce language switching in bilingual patients. *Brain & Language* 2005; **94**(3): 274-277.

Huang C-C, Su T-P, Wei I-H. Repetitive transcranial magnetic stimulation for treating medication-resistant depression in Taiwan: A preliminary study. *Journal of the Chinese Medical Association: JCMA* 2005; **68**(5): 210-215.

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Li X, Nahas Z, Anderson B, Kozel FA, George MS. Can left prefrontal rTMS be used as a maintenance treatment for bipolar depression? *Depression & Anxiety* 2004; **20**(2): 98-100.

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control pilot study of safety and efficacy. *Journal of Neurology, Neurosurgery & Psychiatry* 1999; **67**(1): 113-115.

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Nadeau SE, McCoy KJ, Crucian GP, Greer RA, Rossi F, Bowers D, Goodman WK, Heilman KM, Triggs WJ. Cerebral blood flow changes in depressed patients after treatment with repetitive transcranial magnetic stimulation: evidence of individual variability. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology* 2002; **15**(3): 159-175.

Nahas Z, Bohning DE, Molloy MA, Oustz JA, Risch SC, George MS. Safety and feasibility of repetitive transcranial magnetic stimulation in the treatment of anxious depression in pregnancy: a case report. *Journal of Clinical Psychiatry* 1999; **60**(1): 50-52.

Nahas Z, Li X, Kozel FA, Mirzki D, Memon M, Miller K, Yamanaka K, Anderson B, Chae JH, Bohning DE, Mintzer J, George MS. Safety and benefits of distance-adjusted prefrontal transcranial magnetic stimulation in depressed patients 55-75 years of age: a pilot study. *Depression & Anxiety* 2004; **19**(4): 249-256.

O'Connor MG, Jerskey BA, Robertson EM, Brenninkmeyer C, Ozdemir E, Leone AP. The effects of repetitive transcranial magnetic stimulation (rTMS) on procedural memory and dysphoric mood in patients with major depressive disorder. *Cognitive & Behavioral Neurology* 2005; **18**(4): 223-227.

O'Reardon JP, Blumner KH, Peshek AD, Pradilla RR, Pimiento PC. Long-term maintenance therapy for major depressive disorder with rTMS. *Journal of Clinical Psychiatry* 2005; **66**(12): 1524-1528.

Ogden M, Lyndon W, Pridmore S. Repetitive transcranial magnetic stimulation (rTMS) in major depressive episode with postpartum onset: A case study. *German Journal of Psychiatry* 1999; **2**(1): 43-45.

Padberg F, Zwanzger P, Keck ME, Kathmann N, Mikhaiel P, Ella R, Rupprecht P, Thoma H, Hampel H, Toschi N, Moller HJ. Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. *Neuropsychopharmacology* 2002; **27**(4): 638-645.

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Tharayil BS, Gangadhar BN, Thirthalli J, Anand L. Seizure with single-pulse transcranial magnetic stimulation in a 35-year-old otherwise-healthy patient with bipolar disorder. *Journal of Ect* 2005; **21**(3): 188-189.

Triggs WJ, McCoy KJ, Greer R, Rossi F, Bowers D, Kortenkamp S, Nadeau SE, Heilman KM, Goodman WK. Effects of left frontal transcranial magnetic stimulation on depressed mood, cognition, and corticomotor threshold. *Biological Psychiatry* 1999; **45**(11): 1440-1446.

Zanardini R, Gazzoli A, Ventriglia M, Perez J, Bignotti S, Maria RP, Gennarelli M, Bocchio-Chiavetto L. Effect of repetitive transcranial magnetic stimulation on serum brain derived neurotrophic factor in drug resistant depressed patients. *Journal of Affective Disorders* 2006; **91**(1): 83-86.

Zwanzger P, Ella R, Keck ME, Rupprecht R, Padberg F. Occurrence of delusions during repetitive transcranial magnetic stimulation (rTMS) in major depression. *Biological Psychiatry* 2002; **51**(7): 602-603.

Zwanzger P, Baghai TC, Padberg F, Ella R, Minov C, Mikhaiel P, Schule C, Thoma H, Rupprecht R. The combined dexamethasone-CRH test before and after repetitive transcranial magnetic stimulation (rTMS) in major depression. *Psychoneuroendocrinology* 2003; **28**(3): 376-385.

Appendix D Studies excluded from the review

Study ID	Reason for exclusion
J. M. Abarbanel, T. Lemberg, U. Yaroslavski, N. Grisaru, and R. H. Belmaker. Electrophysiological responses to transcranial magnetic stimulation in depression and schizophrenia. *Biological Psychiatry* 40 (2):148-150, 1996.	Not therapeutic
G. Abraham Combined transcranial magnetic stimulation and right unilateral electroconvulsive therapy in patients with treatment-refractory depression. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie* 2004; 49(6): 412.	rTMS and ECT as combined treatments
P. Alonso, J. Pujol, N. Cardoner, L. Benlloch, J. Deus, J. M. Menchon, A. Capdevila, and J. Vallejo. Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: A double-blind, placebo-controlled study. *American Journal of Psychiatry* 158 (7):1143-1145, 2001.	Not for depression (Obsessive compulsive disorder)
R. Amiaz, O. Stein, S. Schreiber, P. N. Danon, O. T. Dolberg, and L. Grunhaus. Magnetic and seizure thresholds before and after six electroconvulsive treatments. *Journal of Ect* 17 (3):195-197, 2001.	Not therapeutic
B. Aouizerate, C. Martin-Guehl, E. Cuny, D. Guehl, H. Amieva, A. Benazzouz, C. Fabrigoule, B. Bioulac, J. Tignol, and P. Burbaud. Deep brain stimulation for OCD and major depression. *American Journal of Psychiatry* 162 (11):2192-2193, 2005.	Not TMS
M. Bajbouj, A. Luborzewski, H. Danker-Hopfe, and U. E. Lang. Motor cortical excitability in depressive patients after electroconvulsive therapy and repetitive transcranial magnetic stimulation. *Journal of Ect* 21 (4):243-245, 2005.	Not therapeutic
M. Bajbouj, U. E. Lang, P. Neu, and I. Heuser. Therapeutic brain stimulation and cortical excitability in depressed patients. *American Journal of Psychiatry* 162 (11):2192-2193, 2005.	Not TMS
M. Bajbouj, S. H. Lisanby, U. E. Lang, H. Danker-Hopfe, I. Heuser, and P. Neu. Evidence for impaired cortical inhibition in patients with unipolar major depression. *Biological Psychiatry* 59 (5):395-400, 2006.	Not therapeutic
J. Barrett, V. Della-Maggiore, P. A. Chouinard, and T. Paus. Mechanisms of action underlying the effect of repetitive transcranial magnetic stimulation on mood: Behavioral and brain imaging studies. *Neuropsychopharmacology* 29 (6):1172-1189, 2004.	Healthy volunteers
T. Baumer, R. Lange, J. Liepert, C. Weiller, H. R. Siebner, J. C. Rothwell, and A. Munchau. Repeated premotor rTMS leads to cumulative plastic changes of motor cortex excitability in humans. *Neuroimage* 20 (1):550-560, 2003.	Healthy volunteers
F. Bermpohl, F. Fregni, P. S. Boggio, G. Thut, G. Northoff, P. T. M. Otachi, S. P. Rigonatti, M. A. Marcolin, and A. Pascual-Leone. Effect of low-frequency transcranial magnetic stimulation on an affective go/no-go task in patients with major depression: Role of stimulation site and depression severity. *Psychiatry Research* 141 (1):1-13, 2006.	Not therapeutic
R. Boechat-Barros. Low frequency transcranial magnetic stimulation for treatment of depression [Portugese]. *Revista de Psiquiatria Clinica* 31 (5):238-242, 2004.	Not English language
N. N. Boutros, R. M. Berman, R. Hoffman, A. P. Miano, D. Campbell, and R. Ilmoniemi. Electroencephalogram and repetitive transcranial magnetic stimulation. *Depression & Anxiety* 12 (3):166-169, 2000.	Not therapeutic

N. N. Boutros, A. P. Miano, R. E. Hoffman, and R. M. Berman. EEG monitoring in depressed patients undergoing repetitive transcranial magnetic stimulation. *Journal of Neuropsychiatry & Clinical Neurosciences* 13 (2):197-205, 2001.	Not therapeutic
J. P. Brasil-Neto, R. Boechat-Barros, and D. A. Mota-Silveira. The use of slow-frequency transcranial magnetic stimulation in the treatment of depression at Brasilia University Hospital: Preliminary findings. [Portuguese]. *Arquivos de Neuro-Psiquiatria* 61 (1):83-86, 2003.	Not English language
A.V. Chistyakov, B. Kaplan, O. Rubichek, I. Kreinin, D. Koren, H. Hafner, M. Feinsod, E. Klein. Effect of electroconvulsive therapy on cortical excitability in patients with major depression: a transcranial magnetic stimulation study. *Clinical Neurophysiology* 2005; 116(2): 386-392.	rTMS and ECT as combined treatments
R. Chen, C. Gerloff, J. Classen, E. M. Wassermann, M. Hallett, and L. G. Cohen. Safety of different inter-train intervals for repetitive transcranial magnetic stimulation and recommendations for safe ranges of stimulation parameters. *Electromyography and Motor Control-Electroencephalography and Clinical Neurophysiology* 105 (6):415-421, 1997.	Healthy volunteers
E. Chroni, N. P. Lekka, I. Tsoussis, A. Nikolakopoulou, C. Paschalis, and S. Beratis. Effect of exercise on motor evoked potentials elicited by transcranial magnetic stimulation in psychiatric patients. *Journal of Clinical Neurophysiology* 19 (3):240-244, 2002.	Not therapeutic
L. Clark, S. F. B. McTavish, C. J. Harmer, K. R. Mills, P. J. Cowen, and G. M. Goodwin. Repetitive transcranial magnetic stimulation to right prefrontal cortex does not modulate the psychostimulant effects of amphetamine. *International Journal of Neuropsychopharmacology* 3 (4):297-302, 2000.	Healthy volunteers
H. Cohen, Z. Kaplan, M. Kotler, I. Kouperman, R. Moisa, and N. Grisaru. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. *American Journal of Psychiatry* 161 (3):515-524, 2004.	Not for depression (posttraumatic stress disorder)
A. Conca, E. Swoboda, P. Konig, S. Koppi, W. Beraus, A. Kunz, H. Fritzsche, and P. Weiss. Clinical impacts of single transcranial magnetic stimulation (sTMS) as an add-on therapy in severely depressed patients under SSRI treatment. *Human Psychopharmacology* 15 (6):429-438, 2000.	sTMS, not rTMS
A. B. Conforto, W. J. Z'Graggen, A. S. Kohl, K. M. Rosler, and A. Kaelin-Lang. Impact of coil position and electrophysiological monitoring on determination of motor thresholds to transcranial magnetic stimulation. *Clinical Neurophysiology* 115 (4):812-819, 2004.	Not therapeutic (healthy volunteer)
A. Erfurth, N. Michael, C. Mostert, and V. Arolt. Euphoric mania and rapid transcranial magnetic stimulation. *American Journal of Psychiatry* 157 (5):835-836, 2000.	Not for depression (mania)
K. Fujita and Y. Koga. Clinical application of single-pulse transcranial magnetic stimulation for the treatment of depression. *Psychiatry & Clinical Neurosciences* 59 (4):425-432, 2005.	sTMS, not rTMS
V. Geller, N. Grisaru, J. M. Abarbanel, T. Lemberg, and R. H. Belmaker. Slow magnetic stimulation of prefrontal cortex in depression and schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 21 (1):105-110, 1997.	sTMS, not rTMS
M. S. George, L. E. Stallings, A. M. Speer, Z. Nahas, K. M. Spicer, D. J. Vincent, D. E. Bohning, K. T. Cheng, M. Molloy, C. C. Teneback, and S. C. Risch. Prefrontal repetitive transcranial magnetic stimulation (rTMS) changes relative perfusion locally and remotely. *Human Psychopharmacology-Clinical and Experimental* 14 (3):161, 1999.	Not therapeutic (healthy volunteers)
B. D. Greenberg, J. Martin, G. Cora-Locatelli, E. M. Wasserman, J. Grafman, T. A. Kimbrell, T. E. Schlaepfer, M. S. George, F. Jacobsen, R. L. Post, and D. L.	Not therapeutic

Murphy. Effects of single treatment with repetitive transcranial magnetic stimulation (RTMS) at different brain sites in depression. *Electroencephalography and Clinical Neurophysiology* 103 (1):77, 1997.	
N. Grisaru, B. Chudakov, Y. Yaroslavsky, and R. H. Belmaker. Transcranial magnetic stimulation in mania: a controlled study. *American Journal of Psychiatry* 155 (11):1608-1610, 1998.	Not for depression (mania)
A. Hausmann, G. Kemmler, M. Walpoth, S. Mechtcheriakov, K. Kramer-Reinstadler, T. Lechner, T. Walch, E. A. Deisenhammer, M. Kofler, C. I. Rupp, H. Hinterhuber, and A. Conca. No benefit derived from repetitive transcranial magnetic stimulation in depression: a prospective, single centre, randomised, double blind, sham controlled "add on" trial. *Journal of Neurology, Neurosurgery & Psychiatry* 75 (2):320-322, 2004.	Clinical outomes reported separately (Hausmann 2004 J Clin Psych 65:772-782)
U. Herwig, F. Padberg, J. Unger, M. Spitzer, and C. Schonfeldt-Lecuona. Transcranial magnetic stimulation in therapy studies: Examination of the reliability of 'standard' coil positioning by neuronavigation. *Biological Psychiatry* 50 (1):58-61, 2001.	Not therapeutic
Y. Z. Huang and J. C. Rothwell. The effect of short-duration bursts of high-frequency, low-intensity transcranial magnetic stimulation on the human motor cortex. *Clinical Neurophysiology* 115 (5):1069-1075, 2004.	Not therapeutic (healthy volunteers)
H. Jing, M. Takigawa, H. Okamura, W. Doi, and H. Fukuzako. Comparisons of event-related potentials after repetitive transcranial magnetic stimulation. *Journal of Neurology* 248 (3):184-192, 2001.	Not therapeutic (healthy volunteers)
R. E. Jorge, R. G. Robinson, A. Tateno, K. Narushima, L. Acion, D. Moser, S. Arndt, and E. Chemerinski. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: A preliminary study. *Biological Psychiatry* 55 (4):398-405, 2004.	Depression with a co-morbidity (post-stroke)
A. Kaptsan, Y. Yaroslavsky, J. Applebaum, R. H. Belmaker, and N. Grisaru. Right prefrontal TMS versus sham treatment of mania: a controlled study. *Bipolar Disorders* 5 (1):36-39, 2003.	Not for depression (mania)
E. Klein, Y. Kolsky, M. Puyerovsky, D. Koren, A. Chistyakov, and M. Feinsod. Right prefrontal slow repetitive transcranial magnetic stimulation in schizophrenia: a double-blind sham-controlled pilot study. *Biological Psychiatry* 46 (10):1451-1454, 1999.	Not for depression (schizophrenia)
S. Knecht, J. Sommer, M. Deppe, and O. Steinstrater. Scalp position and efficacy of transcranial magnetic stimulation. *Clinical Neurophysiology* 116 (8):1988-1993, 2005.	Not therapeutic (healthy volunteer)
F. A. Kozel, Z. Nahas, C. DeBrux, M. Molloy, J. P. Lorberbaum, D. Bohning, S. C. Risch, and M. S. George. How coil-cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. *Journal of Neuropsychiatry & Clinical Neurosciences* 12 (3):376-384, 2000.	Not therapeutic
X. Li, Z. Nahas, M. Lomarev, S. Denslow, A. Shastri, D. E. Bohning, and M. S. George. Prefrontal cortex transcranial magnetic stimulation does not change local diffusion: a magnetic resonance imaging study in patients with depression. *Cognitive & Behavioral Neurology* 16 (2):128-135, 2003.	Not therapeutic
X. Li, Z. Nahas, F. A. Kozel, B. Anderson, D. E. Bohning, and M. S. George. Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. *Biological Psychiatry* 55 (9):882-890, 2004.	Not therapeutic
S. H. Lisanby, B. Luber, T. E. Schlaepfer, and H. A. Sackeim. Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy.	Deliberate seizure induction

Neuropsychopharmacology 28 (10):1852-1865, 2003.	
C. K. Loo, P. S. Sachdev, W. Haindl, W. Wen, P. B. Mitchell, V. M. Croker, and G. S. Malhi. High (15 Hz) and low (1 Hz) frequency transcranial magnetic stimulation have different acute effects on regional cerebral blood flow in depressed patients. *Psychological Medicine* 33 (6):997-1006, 2003.	Not therapeutic
C. K. Loo, J. L. Taylor, S. C. Gandevia, B. N. McDarmont, P. B. Mitchell, and P. S. Sachdev. Transcranial magnetic stimulation (TMS) in controlled treatment studies: Are some "sham" forms active? *Biological Psychiatry* 47 (4):325-331, 2000.	Healthy volunteers
K. Machii, D. Cohen, C. Ramos-Estebanez, and A. Pascual-Leone. Safety of rTMS to non-motor cortical areas in healthy participants and patients. *Clinical Neurophysiology* 117 (2):455-471, 2006.	Healthy volunteers, review
F. Maeda, J. P. Keenan, and A. Pascual-Leone. Interhemispheric asymmetry of motor cortical excitability in major depression as measured by transcranial magnetic stimulation. *British Journal of Psychiatry* 177:169-173, 2000.	Not therapeutic
P. Manganotti, M. Bortolomasi, G. Zanette, T. Pawelzik, M. Giacopuzzi, and A. Fiaschi. Intravenous clomipramine decreases excitability of human motor cortex. A study with paired magnetic stimulation. *Journal of the Neurological Sciences* 184 (1):27-32, 2001.	Not therapeutic
N. Michael and A. Erfurth. Treatment of bipolar mania with right prefrontal rapid transcranial magnetic stimulation. *Journal of Affective Disorders* 78 (3):253-257, 2004.	Bipolar with mania
A. Mobascher, J. Boecker, J. Malevani, M. Arends, A. Klimke, and J. Cordes. Repetitive transcranial magnetic stimulation as an antidepressant monotherapy in a patient with major depression, leucocytopenia and rhabdomyolysis. *International Journal of Neuropsychopharmacology* 7 (4):527-529, 2004.	Co-morbidities
S. Nedjat and H. W. Folkerts. Induction of a reversible state of hypomania by rapid-rate transcranial magnetic stimulation over the left prefrontal lobe. *Journal of Ect* 15 (2):166-168, 1999.	Healthy volunteers
M. A. Nitsche, D. Liebetanz, F. Tergau, and W. Paulus. [Modulation of cortical excitability by transcranial direct current stimulation]. *Nervenarzt* 73 (4):332-335, 2002.	Not English language
F. Padberg, G. Juckel, A. Prassl, P. Zwanzger, P. Mavrogiorgou, U. Hegerl, H. Hampel, and H. J. Moller. Prefrontal cortex modulation of mood and emotionally induced facial expressions: A transcranial magnetic stimulation study. *Journal of Neuropsychiatry and Clinical Neurosciences* 13 (2):206-212, 2001.	Healthy volunteers
W. Peschina, A. Conca, P. Konig, H. Fritzsche, and W. Beraus. Low frequency rTMS as an add-on antidepressive strategy: heterogeneous impact on 99mTc-HMPAO and 18 F-FDG uptake as measured simultaneously with the double isotope SPECT technique. Pilot study. *Nuclear Medicine Communications* 22 (8):867-873, 2001.	Not therapeutic
S. Pridmore. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in a course of electroconvulsive therapy. *Depression & Anxiety* 2000 (b); 12(3): 118-123.	rTMS and ECT as combined treatments
H. Quintana. Transcranial magnetic stimulation in persons younger than the age of 18. [Review]. Journal of Ect 21 (2):88-95, 2005.	Review
P. D. Reid, B. Daniels, M. Rybak, Y. Turnier-Shea, and S. Pridmore. Cortical excitability of psychiatric disorders: reduced post-exercise facilitation in depression compared to schizophrenia and controls. *Australian & New Zealand Journal of Psychiatry* 36 (5):669-673, 2002.	Not therapeutic

M. Rohan, A. Parow, A. L. Stoll, C. Demopulos, S. Friedman, S. Dager, J. Hennen, B. M. Cohen, and P. F. Renshaw. Low-field magnetic stimulation in bipolar depression using an MRI-based stimulator. *American Journal of Psychiatry* 161 (1):93-98, 2004.	Not rTMS (MRSI)
M. A. Rosa, M. Odebrecht, S. P. Rigonatti, and M. A. Marcolin. Magnetic convulsive therapy: Seizure induction with TMS. [Portuguese]. *Revista de Psiquiatria Clinica* 31 (5):262-265, 2004.	Not English language
D. O. Rumi, B. B. Ortiz, and M. A. Marcolin. Repetitive transcranial magnetic stimulation associated with antidepressant: Start and intensive of the antidrepressant answer. [Portuguese]. *Revista de Psiquiatria Clinica* 31 (5):231-237, 2004.	Not English language
A. Santoro, M. Florita, D. Rossini, F. Benedetti, and A. Lucca. The processing of emotional stimuli in subjects with a major depression episode treated with rTMS. *Clinical Neuropsychiatry: Journal of Treatment Evaluation* 2 (3):183-188, 2005.	Not therapeutic
P. M. Shajahan, M. F. Glabus, J. A. Jenkins, and K. P. Ebmeier. Postexercise motor evoked potentials in depressed patients, recovered depressed patients, and controls. *Neurology* 53 (3):644-646, 1999.	Not therapeutic
E. A. M. Schouten, A. A. L. d'Alfonso, W. A. Nolen, E. H. F. de Haan, J. Wijkstra, and R. S. Kahn. Small effect of rapid rate transcranial magnetic stimulation on antidepressant free outpatients with a depressive disorder. A pilot study. [Dutch]. *Tijdschrift voor Psychiatrie* 41 (4):233-237, 1999.	Not English language
D. J. L. G. Schutter, J. van Honk, A. A. D'Alfonso, A. Postma, and E. H. de Haan. Effects of slow rTMS at the right dorsolateral prefrontal cortex on EEG asymmetry and mood. *Neuroreport* 12 (3):445-447, 2001.	Healthy volunteers
M. Sekino and S. Ueno. Comparison of current distributions in electroconvulsive therapy and transcranial magnetic stimulation. *Journal of Applied Physics* 91 (10):8730-8732, 2002.	Not therapeutic
P. M. Shajahan, M. F. Glabus, J. A. Jenkins, and K. P. Ebmeier. Postexercise motor evoked potentials in depressed patients, recovered depressed patients, and controls. *Neurology* 53 (3):644-646, 1999.	Not therapeutic
H. R. Siebner, M. Peller, F. Willoch, S. Minoshima, H. Boecker, C. Auer, A. Drzezga, B. Conrad, and P. Bartenstein. Lasting cortical activation after repetitive TMS of the motor cortex - A glucose metabolic study. *Neurology* 54 (4):956-963, 2000.	Healthy volunteers
H. R. Siebner, N. Lang, V. Rizzo, M. A. Nitsche, W. Paulus, R. N. Lemon, and J. C. Rothwell. Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: Evidence for homeostatic plasticity in the human motor cortex. *Journal of Neuroscience* 24 (13):3379-3385, 2004.	Healthy volunteers
S. Smesny, H. P. Volz, J. Liepert, R. Tauber, A. Hochstetter, and H. Sauer. [Repetitive transcranial magnetic stimulation (rTMS) in the acute and long-term therapy of refractory depression - a case report]. [German]. *Nervenarzt* 72 (9):734-738, 2001.	Not English language
M. Sommer, A. Dieterich, E. Ruther, W. Paulus, and J. Wiltfang. Increased transcranial magnetic motor threshold after ECT. A case report. *European Archives of Psychiatry & Clinical Neuroscience* 252 (5):250-252, 2002.	Not therapeutic
J. D. Steele, M. F. Glabus, P. M. Shajahan, and K. P. Ebmeier. Increased cortical inhibition in depression: a prolonged silent period with transcranial magnetic stimulation (TMS). *Psychological Medicine* 30 (3):565-570, 2000.	Not therapeutic
N. I. Stikhina, E. B. Lyskov, M. P. Lomarev, Z. A. Aleksanian, V. O. Mikhailov, and S. V.	Not English language

Medvedev. [Transcranial magnetic stimulation in neurotic depression]. [Russian]. *Zhurnal Nevrologii i Psikhiatrii Imeni S* Korsakova. (10):26-29, 1999.	
C. C. Teneback, Z. Nahas, A. M. Speer, M. Molloy, L. E. Stallings, K. M. Spicer, S. C. Risch, and M. S. George. Changes in prefrontal cortex and paralimbic activity in depression following two weeks of daily left prefrontal TMS. *Journal of Neuropsychiatry & Clinical Neurosciences* 11 (4):426-435, 1999.	Complete information reported in Nahas et al 2001
E. M. Wassermann, F. R. Wedegaertner, U. Ziemann, M. S. George, and R. Chen. Crossed reduction of human motor cortex excitability by 1-Hz transcranial magnetic stimulation. *Neuroscience Letters* 250 (3):141-144, 1998.	Healthy volunteers
T. Wu, M. Sommer, F. Tergau, and W. Paulus. Lasting influence of repetitive transcranial magnetic stimulation on intracortical excitability in human subjects. *Neuroscience Letters* 287 (1):37-40, 2000.	Healthy volunteers
X. M. Zheng. Regional cerebral blood flow changes in drug-resistant depressed patients following treatment with transcranial magnetic stimulation: a statistical parametric mapping analysis. *Psychiatry Research* 100 (2):75-80, 2000.	Complete information reported in Loo et al 1999

Appendix E Rating scales for depression

The Hamilton depression rating scale

The Hamilton depression rating scale (HDRS) scale is designed for use in assessing the severity of symptoms of patients with depression. This rating is carried out by the clinician. The first 17 questions contribute to the total score. Questions 18-21 are recorded to give further information about the depression.

Table 40 The Hamilton depression rating scale

1. Depressed mood (sadness, hopelessness, helplessness, worthlessness)
    - 0 Absent
    - 1 These feeling states indicated only on questioning
    - 2 These feeling states reported verbally
    - 3 Communicates feeling states nonverbally (ie facial expression, posture, tendency to weep)
    - 4 Reports only these feeling states in spontaneous verbal and nonverbal communication
2. Feelings of guilt
    - 0 Absent
    - 1 Self-reproach, feels he/she has let people down
    - 2 Ideas of guilt or rumination over past errors or sinful deeds
    - 3 Present illness is a punishment; delusions of guilt
    - 4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations
3. Suicide
    - 0 Absent
    - 1 Feels life is not worth living
    - 2 Wishes he/she were dead or has any thoughts of possible death to self
    - 3 Suicidal ideas or gestures
    - 4 Attempts at suicide (any serious attempt rates “4”)
4. Insomnia – Early
    - 0 No difficulty falling asleep
    - 1 Complains of occasional difficulty falling asleep (ie >1/2 hour)
    - 2 Complains of nightly difficulty falling asleep
5. Insomnia – Middle
    - 0 Absent
    - 1 No difficulty
    - 2 Complains of being restless and disturbed during the night
    - 3 Wakes during the night – getting out of bed rates “2” (except for purposes of voiding)
6. Insomnia – Late
    - 0 No difficulty
    - 1 Wakes in early hours of morning but falls back asleep
    - 2 Unable to fall asleep again if he/she gets out of bed
7. Work and activities
    - 0 No difficulty
    - 1 Thoughts of incapacity; fatigue or weakness related to activities, work or hobbies
    - 2 Loss of interest in activity, hobbies or work
    - 3 Decrease in actual time spent in activities or decrease in productivity
    - 4 Stopped working because of present illness
8. Retardation - (slowness of thought and speech; impaired ability to concentrate; decreased motor activity)
    - 0 Normal speech and thought
    - 1 Slight retardation at interview
    - 2 Oblivious retardation at interview
    - 3 Interview difficult
    - 4 Complete stupor
9. Agitation
    - 0 None
    - 1 Fidgetiness
    - 2 “Playing with” hands, hair, etc
    - 3 Moving about, can’t sit still

4 Hand wringing, nail biting, hair pulling, lip biting

10. Anxiety – Psychic
    - 0 No difficulty
    - 1 Subjective tension and irritability
    - 2 Worries about minor matters
    - 3 Apprehensive attitude apparent in face or speech
    - 4 Fears expressed without questioning
11. Anxiety – Somatic
    - 0 Absent
    - 1 Mild
    - 2 Moderate
    - 3 Severe
    - 4 Incapacitating
12. Somatic symptoms – Gastrointestinal
    - 0 None
    - 1 Loss of appetite, but eating; heavy feeling in abdomen
    - 2 Difficulty eating without urging; requests or requires laxatives or medication for bowels or medication for GI symptoms
13. Somatic symptoms – General
    - 0 None
    - 1 Heaviness in limbs, back of head; backache, headache, muscle ache; loss of energy and fatigue
    - 2 Any clear-cut symptoms rate"2"
14. Genital symptoms (ie loss of libido, menstrual disturbances)
    - 0 Absent
    - 1 Mild
    - 2 Severe
15. Hypochondriasis
    - 0 Not present
    - 1 Self-absorption (bodily)
    - 2 Preoccupation with health
    - 3 Frequent complaints, requests for help, etc.
    - 4 Hypochondriacal delusions
16. Weight loss
    - 0 No weight loss
    - 1 Slight or doubtful weight loss
    - 2 Obvious or severe weight loss
17. Insight
    - 0 Acknowledges being depressed or ill
    - 1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
    - 2 Denies being ill at all
18. Diurnal variation
    - 0 No variation
    - 1 Mild: doubtful or slight variation
    - 2 Severe: clear or marked variation; if applicable, note whether symptoms are worse in AM( ) or PM( )
19. Depersonalization and derealization (feelings of unreality, nihilistic ideas)
    - 0 Absent
    - 1 Mild
    - 2 Moderate
    - 3 Severe
    - 4 Incapacitating
20. Paranoid symptoms
    - 0 None
    - 1 Suspicious
    - 2 Ideas of reference
    - 3 Delusions of reference or persecution
    - 4 Paranoid hallucinations
21. Obsessive/compulsive symptoms
    - 0 Absent
    - 1 Mild
    - 2 Severe

The GlaxoSmithKline Group of Companies; *Adapted from Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.

The Beck depression inventory

The Beck depression inventory is a 21-question multiple choice survey that is one of the most widely used instruments for measuring the severity of depression. The questionnaire is patient-rated, and is composed of items relating to depression symptoms such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue.

Table 41 The Beck depression inventory

1		
	0	I do not feel sad.
	1	I feel sad.
	2	I am sad all the time and I can't snap out of it.
	3	I am so sad or unhappy that I can't stand it
2		
	0	I am not particularly discouraged about the future
	1	I feel discouraged about the future.
	2	I feel I have nothing to look forward to.
	3	I feel that the future is hopeless and that things cannot improve
3		
	0	I do not feel like a failure.
	1	I feel I have failed more than the average person.
	2	As I look back on my life, all I can see is a lot of failure
	3	I feel I am a complete failure as a person
4		
	0	I get as much satisfaction out of things as I used to.
	1	I don't enjoy things the way I used to.
	2	I don't get any real satisfaction out of anything anymore.
	3	I am dissatisfied or bored with everything
5		
	0	I don't feel particularly guilty
	1	I feel guilty a good part of the time.
	2	I feel quite guilty most of the time.
	3	I feel guilty all of the time.
6		
	0	I don't feel I am being punished.
	1	I feel I may be punished.
	2	I expect to be punished.
	3	I feel I am being punished.
7		
	0	I don't feel disappointed in myself.
	1	I am disappointed in myself.
	2	I am disgusted with myself.
	3	I hate myself.
8		
	0	I don't feel I am any worse than anybody else.
	1	I am critical of myself for my weaknesses or mistakes
	2	I blame myself all the time for my faults.
	3	I blame myself for everything bad that happens.
9		
	0	I don't have any thoughts of killing myself
	1	I have thoughts of killing myself, but I would not carry them out
	2	I would like to kill myself.
	3	I would kill myself if I had the chance.
10		
	0	I don't cry any more than usual.
	1	I cry more now than I used to.
	2	I cry all the time now.
	3	I used to be able to cry, but now I can't cry even though I want to.
11		
	0	I am no more irritated by things than I ever am.

1	I am slightly more irritated now than usual
2	I am quite annoyed or irritated a good deal of the time.
3	I feel irritated all the time now.
12	
0	I have not lost interest in other people.
1	I am less interested in other people than I used to be.
2	I have lost most of my interest in other people.
3	I have lost all of my interest in other people.
13	
0	I make decisions about as well as I ever could.
1	I put off making decisions more than I used to.
2	I have greater difficulty in making decisions than before.
3	I can't make decisions at all anymore
14	
0	I don't feel that I look any worse than I used to
1	I am worried that I am looking old or unattractive.
2	I feel that there are permanent changes in my appearance that make me look unattractive
3	I believe that I look ugly.
15	
0	I can work about as well as before.
1	It takes an extra effort to get started at doing something.
2	I have to push myself very hard to do anything.
3	I can't do any work at all.
16	
0	I can sleep as well as usual.
1	I don't sleep as well as I used to.
2	I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3	I wake up several hours earlier than I used to and cannot get back to sleep.
17	
0	I don't get more tired than usual.
1	I get tired more easily than I used to.
2	I get tired from doing almost anything.
3	I am too tired to do anything
18	
0	My appetite is no worse than usual.
1	My appetite is not as good as it used to be.
2	My appetite is much worse now.
3	I have no appetite at all anymore
19	
0	I haven't lost much weight, if any, lately.
1	I have lost more than five pounds.
2	I have lost more than ten pounds.
3	I have lost more than fifteen pounds.
	(Score 0 if you have been purposely trying to lose weight.)
20	
0	I am no more worried about my health than usual.
1	I am worried about physical problems such as aches and pains, or upset stomach, or constipation.
2	I am very worried about physical problems, and it's hard to think of much else.
3	I am so worried about my physical problems that I cannot think about anything else.
21	
0	I have not noticed any recent change in my interest in sex.
1	I am less interested in sex than I used to be.
2	I am much less interested in sex now.
3	I have lost interested in sex completely.

Scoring	
1 – 10	These ups and downs are considered normal.
11 – 16	Mild mood disturbance
17 – 20	Borderline clinical depression
21 – 30	Moderate depression
31 – 40	Severe depression
over 40	Extreme depression

The brief psychiatric rating scale

The brief psychiatric rating scale (BPRS) is a 24-item observer-scale designed to assess patients with major psychiatric disorders, particularly schizophrenia. The BPRS measures positive symptoms, general psychopathology and affective symptoms. It consists of 24 symptom constructs, each to be rated in a 7-point scale of severity ranging from 'not present' (1) to 'extremely severe' (7).

Table 42 The brief psychiatric rating scale

	Symptom	Severity						
		1	2	3	4	5	6	7
1	Somatic concern							
2	Anxiety							
3	Depression							
4	Suicidality							
5	Guilt							
6	Hostility							
7	Elated Mood							
8	Grandiosity							
9	Suspiciousness							
10	Hallucinations							
11	Unusual thought content							
12	Bizarre behaviour							
13	Self-neglect							
14	Disorientation							
15	Conceptual disorganisation							
16	Blunted affect							
17	Emotional withdrawal							
18	Motor retardation							
19	Tension							
20	Uncooperativeness							
21	Excitement							
22	Distractibility							
23	Motor hyperactivity							
24	Mannerisms and posturing							

From Ventura, Green, Shaner & Liberman (1993) Training and quality assurance with the brief psychiatric rating scale: "The drift buster" *International Journal of Methods in Psychiatric Research*.

The global assessment of functioning scale

The global assessment of functioning, or GAF scale, is a numeric scale (0 through 100) used by mental health clinicians and doctors to rate the social, occupational and psychological functioning of adults. The version of the GAF scale shown below is intended for academic use only. Although it is based on the clinical scale presented in the DSM–IV (axis V), this summary lacks the detail and specificity of the original document.

Table 43 The global assessment of functioning scale

Code	Description of functioning
91 - 100	Person has no problems OR has superior functioning in several areas OR is admired and sought after by others due to positive qualities
81 - 90	Person has few or no symptoms. Good functioning in several areas. No more than "everyday" problems or concerns.
71 - 80	Person has symptoms/problems, but they are temporary, expectable reactions to stressors. There is no more than slight impairment in any area of psychological functioning.
61 - 70	Mild symptoms in one area OR difficulty in one of the following: social, occupational, or school functioning. BUT, the person is generally functioning pretty well and has some meaningful interpersonal relationships.
51 - 60	Moderate symptoms OR moderate difficulty in one of the following: social, occupational, or school functioning.
41 - 50	Serious symptoms OR serious impairment in one of the following: social, occupational, or school functioning.
31 - 40	Some impairment in reality testing OR impairment in speech and communication OR serious impairment in several of the following: occupational or school functioning, interpersonal relationships, judgment, thinking, or mood.
21 - 30	Presence of hallucinations or delusions which influence behaviour OR serious impairment in ability to communicate with others OR serious impairment in judgment OR inability to function in almost all areas.
11 - 20	There is some danger of harm to self or others OR occasional failure to maintain personal hygiene OR the person is virtually unable to communicate with others due to being incoherent or mute.
1 - 10	Persistent danger of harming self or others OR persistent inability to maintain personal hygiene OR person has made a serious attempt at suicide.

The Pittsburgh sleep quality index

The Pittsburgh sleep quality index (PSQI) is used to measure the quality and patterns of sleep in the older adult. The client self-rates each of the seven areas of sleep for the majority of days and nights in the past month. Scoring of answers is based on a 0 to 3 scale:

Table 44 The Pittsburgh sleep quality index

Question	Answer			
1. When have you usually gone to bed?				
2. How long (in minutes) has it taken you to fall asleep each night?				
3. When have you usually got out of bed in the morning?				
4. How many hours of actual sleep did you usually get each night?				
5. During the past month, how often have you had trouble sleeping because you…	Not during the past month (0)	Less than once a week (1)	Once or twice a week (2)	Three or more times a week (3)
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom including how often				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Have bad dreams				
i. Have pain				
j. Other reason(s), please describe, you have had trouble sleeping because of this reason(s):				
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?				
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				
8. During the past month, how much of a problem has it been for you to keep up enthusiasm to get things done?				
	Very good (0)	Fairly good (1)	Fairly bad (2)	Very bad (3)
9. During the past month, how would you rate your sleep quality overall?				

Component 1 = #9 Score
Component 2 = #2 Score
(< 15min (0), 16-30 min (1), 31-60 min (2), >60 min (3)) + #5a Score (if sum is equal 0=0; 1-2=1; 3-4=2; 5-6=3)
Component 3 = #4 Score (>7(0), 6-7(1), 5-6(2), <5 (3)
Component 4 = (total # of hours asleep)/(total # of hours in bed) x 100
>85%=0, 75%-84%=1, 65%-74%=2, <65%=3
Component 5 = # sum of scores 5b to 5j (0=0; 1-9=1; 10-18=2; 19-27=3)
Component 6 = #6 Score
Component 7 = #7 score + #8 score (0=0; 1-2=1; 3-4=2; 5-6=3)

The Global PSQI Score is the sum of the seven component scores.

From Journal of Psychiatric Research, 28(2), Buysse, D.J., Reynolds III, C.F., Monk, T.H., Berman, S.R., & Kupfer, D.J. The Pittsburgh Sleep Quality Index: A New Instrument for Psychiatric Practice and Research, 193-213.

The Young mania rating scale

The Young mania rating Scale (YMRS) is an 11-item instrument used to assess the severity of mania in patients with a diagnosis of bipolar disorder. Ratings are based on patient self-reporting, combined with clinician observation (accorded greater score). YMRS features operationally-defined anchor points and the normal expected score is ≥20.

Table 45 The Young mania rating scale

1. Elevated mood	
0	Absent
1	Mildly of possible increased on questioning
2	Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
3	Elevated; inappropriate to content; humorous
4	Euphoric; inappropriate laughter; singing
2. Increased motor activity-energy	
0	Absent
1	Subjectively increased
2	Animated; gestures increased
3	Excessive energy; hyperactive at times; restless (can be calmed)
4	Motor excitement; continuous hyperactivity (cannot be calmed)
3. Sexual interest	
0	Normal; not increased
1	Mildly of possibly increased
2	Definite subjective increase on questioning
3	Spontaneous sexual content; elaborated on sexual matters; hypersexual by self-report
4	Overt sexual acts (towards patients, staff, or interviewer)
4. Sleep	
0	Reports no decrease in sleep
1	Sleeping less than normal amount by up to one hour
2	Sleeping less than normal by more that one hour
3	Reports decreased need for sleep
4	Denies need for sleep
5. Irritability	
0	Absent
1	Subjectively increased
2	Irritable at times during interview; recent episodes of anger or annoyance on ward
3	Frequently irritable during interview; short curt throughout
4	Hostile, unco-operative; interview impossible
6. Speech (rate and amount)	
0	No increase
1	Feels talkative
2	Increased rate or amount at times, verbose at times
3	Push; consistently increased rate and amount difficult to interpret
4	Pressured; uninterruptible, continuous speech
7. Language – thought disorder	
0	Absent

1	Circumstantial; mild distractibility; quick thoughts
2	Distractible; loses goal of thought; changes topics frequently; racing thoughts
3	Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
4	Incoherent; communication impossible
8. Content	
0	Normal
1	Questionable plans, new interests
2	Special project(s)
3	Grandiose or paranoid ideas; ideas of reference
4	Delusions; hallucinations
9. Disruptive-aggressive behaviour	
0	Absent, co-operative
1	Sarcastic; loud at times, guarded
2	Demanding; threats on ward
3	Threatens interviewer; shouting; interview difficult
4	Assaultive; destructive; interview impossible
10. Appearance	
0	Appropriate dress and grooming
1	Minimally unkempt
2	Poorly groomed; moderately dishevelled overdressed
3	Dishevelled; partly clothed; garish make up
4	Completely unkempt; decorated; bizarre garb
11. Insight	
0	Present; admits illness; agrees with need for treatment
1	Possibly ill
2	Admits behaviour change, but denies illness
3	Admits possible change in behaviour, but denies illness
4	Denies any behaviour change

The visual analogue scale

Visual analogue scales (VAS) measure the intensity or magnitude of sensations and subjective feelings, and the relative strength of attitudes and opinions about specific stimuli. For example, the amount of pain that a patient feels ranges across a continuum from none to an extreme amount of pain. From the patient's perspective this spectrum appears continuous and their pain does not take discrete steps, as a categorisation of none, mild, moderate and severe would suggest. It was to capture this idea of an underlying continuum that the VAS was devised.

Operationally a VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient marks on the line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks.

The Wechsler adult intelligence scale

The Wechsler adult intelligence scale (WAIS) is a general test of intelligence (intelligence quotient, IQ), published in February 1955 as a revision of the Wechsler-Bellevue test (1939), standardised for use with adults over the age of 16. Intelligence is quantified as the global capacity of the individual to act purposefully, to think rationally, and to deal effectively with the environment.

The full scale IQ is broken down into 14 subtests, comprising the verbal (7 subtests) and performance scales (7 subtests). Wechsler's tests provide three scores:

1. Verbal IQ.

2. Performance IQ.

3. A composite, single full-scale IQ score based on the combined scores.

Glossary of the cognitive tests

Table 46 Cognitive tests used in the studies

Cognitive Test	Description
Letter number sequencing	The ordering of numbers and letters presented in an unordered sequence. This is a test of working memory.
New learning	Using a 15-item word list (RVLT)
	Acquisition - Free-recall of the 15 words repeated over 5 trials
	Retention - Free recall after a 20 minute delay
	Retrograde memory - Recall of items from the transient news events test (TNET)
Learning	Auditory verbal learning test (AVLT). 15 words are learned before treatment
	Immediate recall
	Recall after interference
	Recall after delay
	Recognition hits
	Recognition false alarms
Memory for person test	A visual memory test in which each of 12 different faces has to be associated with a name and an occupation
	Recall
	Relayed recall
Retrograde memory	Retrograde auditory verbal learning test: serial learning with two sets of related concrete nouns. Tests for difficulty in remembering the past.
	Recall
	Recognition hits
	Recognition false alarms
Four card task	Four picture cards from the Rivermead Behavioral Memory Test. The number, type and arrangement of the cards can be tested
	Recognition
	Free recall
Autobiographical memory interview	Retrograde memory test: tests for amnesia and capacity to remember facts and incidents in earlier life
	Recall score
Subjective memory	Squire subjective memory questionnaire; an 18 item self-rated scale of memory on a 9-point scale
Mini mental state exam	A general test to assesses cognitive mental status
Trail making test A and B	A test of visual conceptual and visuomotor tracking. Patients must track numbers and letters spread randomly across a sheet of paper.
Digit span test	A computerised test where the subject must repeat a digit presented to them. The computer adds a new digit progressively, and records all mistakes.
Letter-number span	The subject must hold and mentally manipulate letter-number sequences.
Word fluency	The ability of the subject to produce as many words as possible in a given category, within a fixed time span.

Appendix F Websites of HTA organisations

AUSTRALIA
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) http://www.surgeons.org/asernip-s.htm
Centre for Clinical Effectiveness, Monash University http://www.med.monash.edu.au/healthservices/cce/evidence/
Health Economics Unit, Monash University http://chpe.buseco.monash.edu.au
AUSTRIA
Institute of Technology Assessment / HTA unit http://www.oeaw.ac.at/ita/e1-3.htm
CANADA
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/en/
Alberta Heritage Foundation for Medical Research (AHFMR) http://www.ahfmr.ab.ca/publications.html
Canadian Coordinating Office for Health Technology Assessment (CCHOTA) http://www.ccohta.ca/entry_e.html
Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca
Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca
DENMARK
Danish Institute for Health Technology Assessment (DIHTA) http://www.dihta.dk/publikationer/index_uk.asp
Danish Institute for Health Services Research (DSI) http://www.dsi.dk/engelsk.html
FINLAND
FINOHTA http://www.stakes.fi/finohta/e/
FRANCE
L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES) http://www.anaes.fr/
GERMANY
German Institute for Medical Documentation and Information (DIMDI) / HTA http://www.dimdi.de/en/hta/index.html
THE NETHERLANDS
Health Council of the Netherlands Gezondheidsraad http://www.gr.nl/adviezen.php
NEW ZEALAND
New Zealand Health Technology Assessment (NZHTA) http://nzhta.chmeds.ac.nz/
NORWAY
Norwegian Centre for Health Technology Assessment (SMM) http://www.oslo.sintef.no/smm/Publications/Engsmdrag/FramesetPublications.htm
SPAIN
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS) http://www.isciii.es/aets/
Catalan Agency for Health Technology Assessment (CAHTA) http://www.aatm.es/cgi-bin/frame.pl/ang/pu.html
SWEDEN
Swedish Council on Technology Assessment in Health Care (SBU) http://www.sbu.se/admin/index.asp
Center for Medical Health Technology Assessment http://www.cmt.liu.se/English/Engstartsida.html
SWITZERLAND
Swiss Network on Health Technology Assessment (SNHTA) http://www.snhta.ch/

UNITED KINGDOM
Health Technology Board for Scotland http://www.htbs.org.uk/
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) http://www.hta.nhsweb.nhs.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD) http://www.york.ac.uk/inst/crd/
National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/index.htm
The Cochrane Library http://www.cochrane.org/reviews/clibaccess.htm
UNITED STATES
Agency for Healthcare Research and Quality (AHRQ) http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health – Cost-Utility Analysis Registry http://www.tufts-nemc.org/cearegistry/index.html
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center
(TEC) http://www.bcbs.com/consumertec/index.html

Appendix G Meta-analyses of rTMS versus sham treatment

Introduction

The economic analysis of rTMS in the treatment of severe depression required consideration of two alternative treatments: treatment with ECT, and anti-depressant medication. ECT is the main comparator for this review and results from meta-analysis of all relevant studies have been reported previously (see Table 20 and Table 21). However, expert opinion of the Advisory Panel suggested that only a minority of patients with treatment-resistant depression (possibly around 5%) receive ECT as a treatment option. The majority of patients with treatment-resistant depression (up to 95%) receive alternate pharmacological of psychological treatments either because of patient refusal or due to treatment preference by the clinician. A significant proportion of patients who refuse ECT may consider rTMS if it was offered as a treatment option. Therefore for the economic analysis of rTMS for depression we will consider the effectiveness of rTMS compared with ECT, and the effectiveness of rTMS compared with anti-depressant medication.

Many studies have been published which investigated the effectiveness of rTMS compared with sham rTMS as a treatment for severe depression (see Appendix C). Sham rTMS is similar to a placebo where the rTMS coil is held at an angle to the head of the subject so that no magnetic stimulation is delivered to the underlying cortex. Alternatively there is a stimulation of the noise of the active coil without any induced magnetic pulses. The patient is blind to this procedure. There are numerous forms of sham rTMS treatment, and it is possible that some sham treatments may have an active effect above that of placebo (Loo et al 2000).

Rationale

Three items of clinical evidence were required for the economic analysis:

1. The response rate of rTMS compared to ECT.
2. The response rate of rTMS compared to sham treatment.
3. The baseline risk for people who are resistant to anti-depressant medication.

The first item has been covered previously in this report (see Figure 2 and Table 20).

The second item is covered in the following section. The meta-analyses of rTMS versus sham treatment were performed to inform the incremental cost-effectiveness (ICER) of the policy of public funding of rTMS for people who are treatment resistant (to anti-depressant medication) and would otherwise have ECT. According to expert opinion from the Advisory Panel, this group represents an estimated 5 per cent of all patients who are treatment resistant. The incremental cost-effectiveness analysis of the policy (as distinct from the

treatment for patients meeting the restriction) recognises that under such a restriction, at least some of the other 95 per cent of treatment resistant patients will also have the treatment subsidised by the MBS.

It is clear that the expected utilisation under the policy will be more than the target group of patients (item drift). It is less obvious that the ICER would also be different for the policy versus the treatment for targeted patients. This will occur for the following reasons:

1. It is expected that the differences in the comparator (ECT for patients meeting the restriction and continued anti-depressant medication or no anti-depressant medication for patients who would have subsidised treatment but not meet restriction) may mean differences in the treatment effect.
2. Baseline risk may differ for the two groups.
3. It is expected that there will be differences in resource use in absence of policy for the two groups, with the target group otherwise having a costly ECT.

The meta-analyses presented in this section address the first estimate – the treatment effect for people who are anti-depressant medication resistant but would otherwise have not had ECT.

Meta-analyses of rTMS versus sham treatment

Search strategy

Forty-four randomised controlled trials reporting the safety and effectiveness of rTMS compared to sham rTMS in the treatment of severe depression were identified (Appendix C). Of these, five did not report depression scores at baseline, or outcome, or both, leaving 39 studies which were included. These studies were identified through the original search strategy for this review (see Approach to assessment), but were excluded from the main review due to the fact that the comparator was not ECT. Data from these RCTs was evaluated using meta-analysis to provide information regarding the effectiveness of rTMS compared to sham treatment (ie no treatment) for the purposes of cost-effectiveness analysis.

The information from the various meta-analyses conducted on these studies is summarised in Table 48.

Summary of results

For mean change in HDRS:

- 39 studies were included.
- The best estimate of the treatment effect is the relative risk (RR) of -3.41 (-3.82, -3.01); that is, the mean change in HDRS for rTMS was 3.41 times greater than the mean change in HDRS for sham.

For response rate:

- Eighteen of the studies included an estimate of response rate.
- The best estimate of the treatment effect as measured by response rate (a 50% or greater reduction in HDRS) is 0.40 (0.3, 0.53); that is, the response rate for sham is 0.40 times that of the response rate for rTMS.
- Nine studies stated that the patients were known to be treatment resistant to anti-depressant medication.
- The best estimate of the treatment effect as measured by response rate (a 50% or greater reduction in HDRS) is 0.36 (0.21, 0.64); that is, the response rate for sham is 0.36 times that of the response rate for rTMS.

The studies that included the response rate had a similar RR for mean change in HDRS compared to the studies that did not have a response rate recorded (-3.91 (-4.49, -3.33) for the former and -3.70 (-4.32, -3.06) for the latter).

In the studies in which there was a follow-up period, the response rate was not maintained by most patients (>75%) after 3 months.

Recommendation:

- That the base case treatment effect for the 'item drift' group is assumed to be 0.36 (ie the response rate for the usual care group is 0.36 that of the response rate for the rTMS group), which is the odds ratio for patients who are known to be treatment resistant.
- That the base case duration of response is assumed to be 3 months.

Comparison with Cochrane meta-analysis

Cochrane published a meta-analysis of the effectiveness of rTMS in the treatment of severe depression in 2001. The 2 week outcome meta-analysis included 8 trials, the most recent of which was published in 2001. The analysis was of the mean HDRS at baseline and at end of treatment. It was not corrected for baseline differences between studies or within study.

We duplicated the Cochrane meta-analysis and found that there was an error in the published analysis – baseline scores for one study were treated as outcome scores. This error accounts for the difference in the results of the published meta-analysis and the duplicate analysis we performed.

Cochrane:
-0.35 (-0.66, -0.04) – ie the HDRS at 2 week outcome for rTMS was 0.35 that of sham.

Our duplication:
-0.43 (-0.75, -0.11) – ie the HDRS at 2 week outcome for rTMS was 0.43 that of Sham.

A further 30 studies were included in the meta-analysis we performed.

Estimate of baseline risk

The baseline risk for people who are resistant to anti-depressant medication is required to complete the three items of clinical evidence required for this economic evaluation (see Rationale above).

Meta-analyses provide estimates of the treatment effect. They do not provide estimates of baseline risks, in this case, usual care response rates. Ideally, these baseline risks are sourced from epidemiological studies; for example, the treatment effect (relative risk reduction) of bisphosphonates are derived from trials and applied to population (not trial) fracture rates.

There is little published evidence which has reported the rates of failure of response to anti-depressant medication in large patient cohorts. A clinician would generally make a choice of therapy for a patient who failed to respond to a first treatment from clinical experience, and not from randomised research (Menza 2006). A recent study (STAR*D) has recently begun starting to publish data from a large multi-centre trial which followed over 4,000 people with non-psychotic major depression over three courses of anti-depressant medication (Fava et al 2006; Trivedi et al 2006 a and b; Rush et al 2006). Although not an epidemiological study, the authors attempted to include a wide range of patients as would be seen in a typical outpatient practice, such that their data is generally applicable to the population as a whole.

Response was defined as a reduction of 50 per cent or more on baseline scores (using the Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR-16)). As shown in Table 47, 37% of all non-psychotic patients with severe depression do not have a complete response to three trials of anti-depressant medication.

Table 47 STAR*D trial results

Level	Treatment description	Response rate	Non-response rate	Cumulative non-response rate
1	Citalopram alone	47%	53%	53%
2	AD switch strategy	27.2% (851)	81.9%	43%
	Or AD augmentation strategy	29.4% (727)		
		28.1% (weighted mean)		
3	Mirtazapine	15.0%	85%	37%
	Or Nortriptyline			

We also need to make estimates of the use of medications during and after the treatment. Our review of the studies suggests that:

- Repetitive transcranial magnetic stimulation is at least as effective and possibility more effective if used as add-on therapy (to anti-depressants).

- Responders to rTMS will continue to use anti-depressants as maintenance.

Advice from the Advisory Panel suggests that anti-depressant medication is changed and continued after ECT treatment, and that this will likely be the case with rTMS.

Additional considerations

While reviewing the 39 studies for the meta-analysis, we noted the following study-specific conclusions. These scenarios may relate to patients who are most likely to be treated with rTMS, in which case they are likely to lower the baseline response rate and the treatment effect compared with the overall group. It is also important to consider the possibility that there will be variation in the specifics of rTMS treatment between different centres: number of cycles, duration of cycles and position of coils. This may also have an effect on the actual response rate.

- Levels of high medication resistance are associated with poorer response to treatment, even with ECT (Avery et al 2006).

- Patients with a shorter duration of depression, including duration of current episode, are more likely to respond to rTMS treatment (George et al 2000; Holtzheimer et al 2004).

- There are still important questions to be answered regarding rTMS treatment, including the exact location of coil placement, choice of treatment frequency and intensity, and which neurobiological parameters may mediate the effect of rTMS (Herwig et al 2003; Nahas et al 2001).

- Repetitive transcranial magnetic stimulation is not associated with negative cognitive functioning (Avery et al 2006; Holtzheimer et al 2004).

- Medication may be needed to maintain treatment effect (Klein et al 1999; George et al 2000).

- Repetitive transcranial magnetic stimulation may work by accelerating the response to anti-depressant medication (Rumi et al 2005).

Table 48 A summary of the meta-analyses conducted for rTMS versus sham treatment

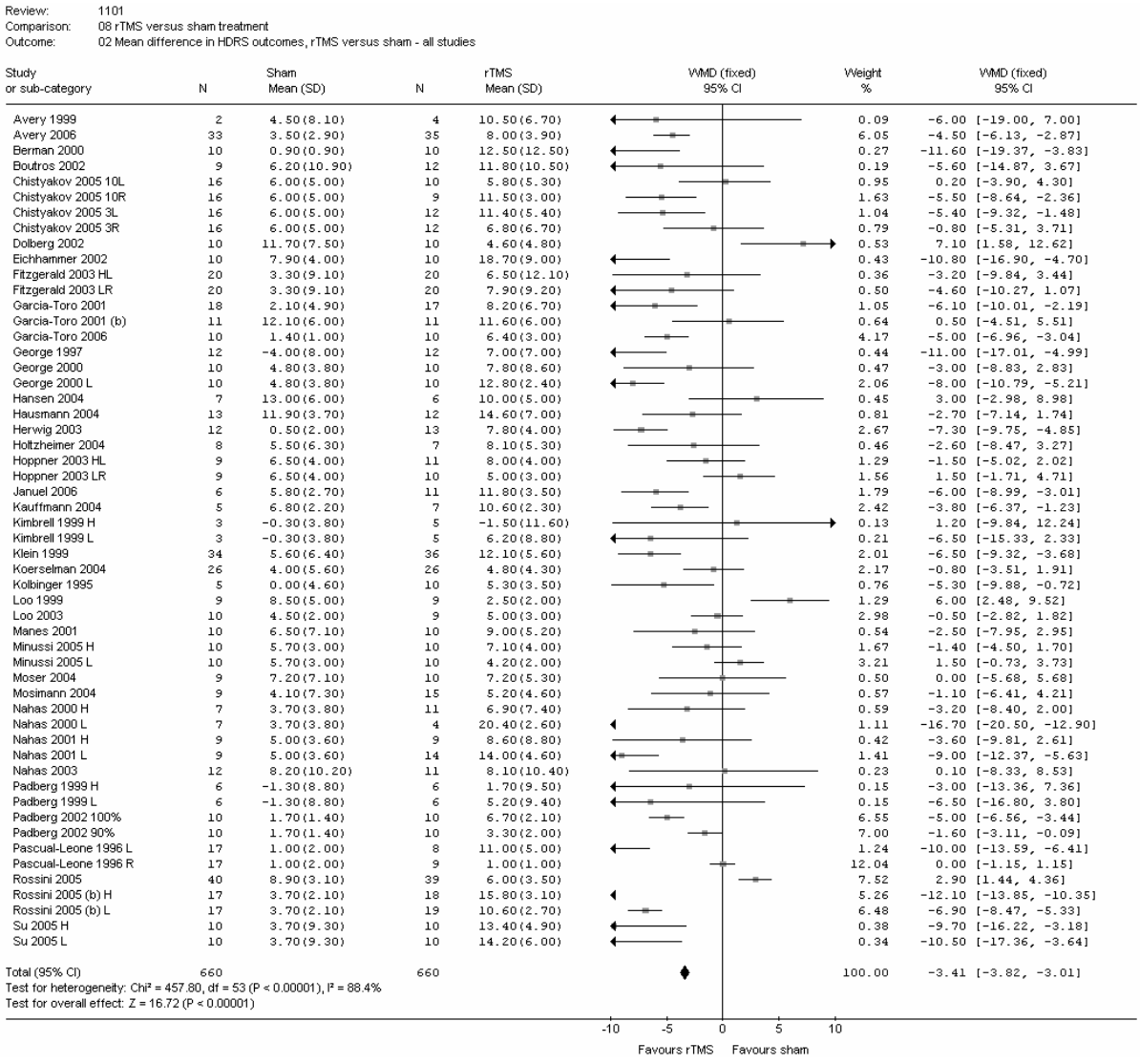
Description	Rationale	Figure number; Number of trials (and patients)	Result
All RCTs of rTMS vs sham; mean difference in HDRS outcome	To investigate any differences between rTMS and sham in the treatment of depression, using effect size of HDRS as the outcome	Figure 20; 39 (and 1135)	For change in HDRS -3.41 (-3.82, -3.01)
All RCTs of rTMS vs sham , where response rate was included as an outcome		Figure 21; 18 (and 570)	For response rate 0.40 (0.3, 0.53)
Sub-meta analyses – by outcome type			
With response rate as an outcome	Do studies which reported response rates as an outcome differ to the total studies?	Figure 21; 17 (and 530)	For change in HDRS -3.91 (-4.49, -3.33)
		Figure 23; 18 (and 570)	For response rate 0.40 (0.3, 0.53)
Without response rate as an outcome	Do studies which did not report response rates as an outcome differ to the total studies?	Figure 22; 22 (and 612)	For change in HDRS -3.70 (-4.32, -3.06)
Sub- meta-analyses – by patient medication	Does response rate differ when patients are removed from medication prior to rTMS?		
Studies where patients had been removed from AD medication		Figure 24; 6 (and 161)	For response rate 0.26 (0.13, 0.54)
Studies with rTMS as and add-on to AD medication		Figure 25; 12 (and 409)	For response rate 0.44 (0.32, 0.61)
Sub-meta-analyses – by medication resistance	Does response rate differ when patients are stated to be anti-depressant medication resistant?		
Studies with patients stated to be medication-resistant		Figure 26; 9 (and 253)	For response rate 0.36 (0.21, 0.64)
Studies with patients stated to be not medication-resistant		Figure 27; 2 (and 50)	For response rate 0.37 (0.15, 0.90)
Cochrane analyses (Martin et al 2001)	Original results	[Not shown] 9 (and 175)	-0.35 (-0.66, -0.04)
	To duplicate results as found in Martin 2001 to confirm the analyses we have done	Figure 27; 8 (and 163)	-0.43 (-0.75, -0.11)
	To repeat the analysis done above but with all currently available studies, to update the Cochrane results	Figure 29; 39 (and 1058)	-0.26 (-0.39, -0.12)

Meta-analyses for effect-size – HDRS as an indicator

Studies were reviewed which used HDRS as the primary outcome. Thirty nine of these trials were included (see Figure 20 and Appendix C). There were 661 patients in rTMS arms and 506 in sham arms. For studies that had more than one type of rTMS treatment, the data were entered in separately for each arm eg Fitzgerald 2003 HL (high frequency left) and LR (low frequency right). The sham values are duplicated for each arm when done this way. The results of this meta-analysis are presented in Figure 20. The meta-analysis was of effect size – the difference between HDRS scores at baseline and end of trial. Where mean effect size and standard deviation of effect size were not reported, mean effect size was calculated and standard deviation of the change was estimated as being the same as the standard deviation at baseline (where reported). The duration of treatment ranged from 1 to 4 weeks. We used the effect size at end of treatment and not at follow-up.

The results were: -3.41 (in favour of rTMS), with confidence intervals (CI) of -3.82, -3.01.

Figure 20 rTMS versus sham for HDRS effect size



The cost-effectiveness analysis requires an estimate of response rate for rTMS versus sham. There is a risk that the studies that reported response rate differed either systematically or randomly from the trials that did not report response rate. To assess this risk we performed a meta-analysis of two sets of studies – those with and those without response rate as an indicator of outcome. The results are presented in Figure 21 and Figure 22.

Relative risks are -3.91 CI (-4.49, -3.33) for studies which have reported response rates and -3.70 CI (-4.43, -3.06) for studies which had not reported response rates. Therefore there was no significant difference between these two categories of studies when effect size of HDRS was considered.

Figure 21 Studies which report response (rTMS versus sham) for HDRS effect size

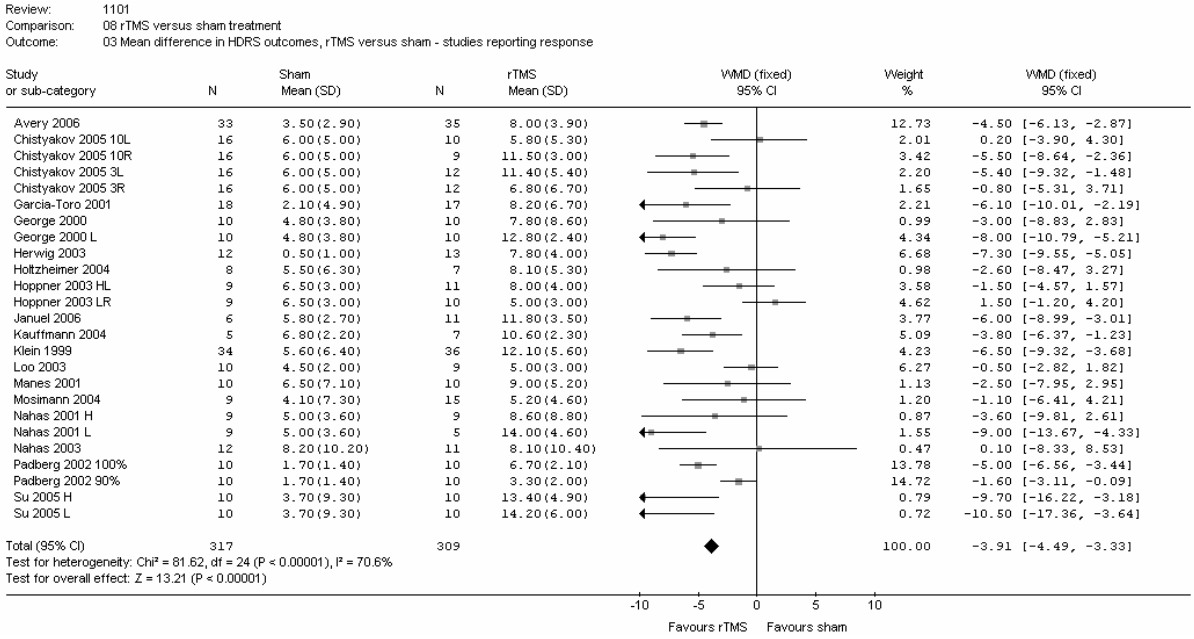
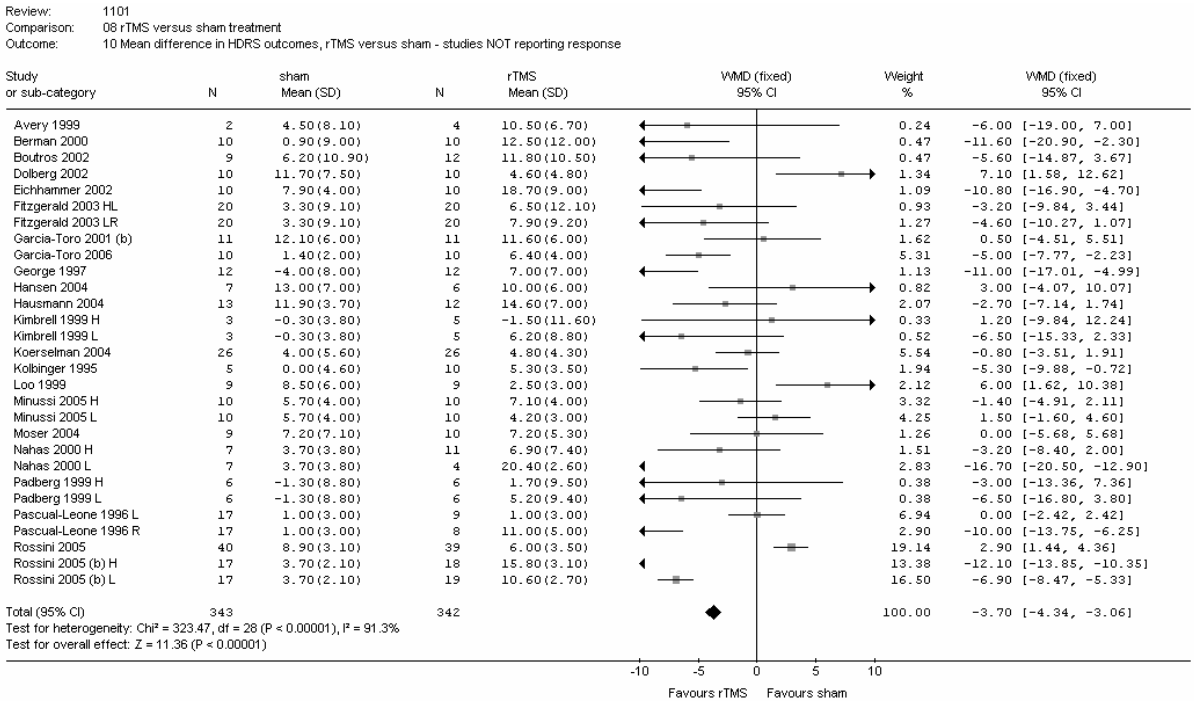


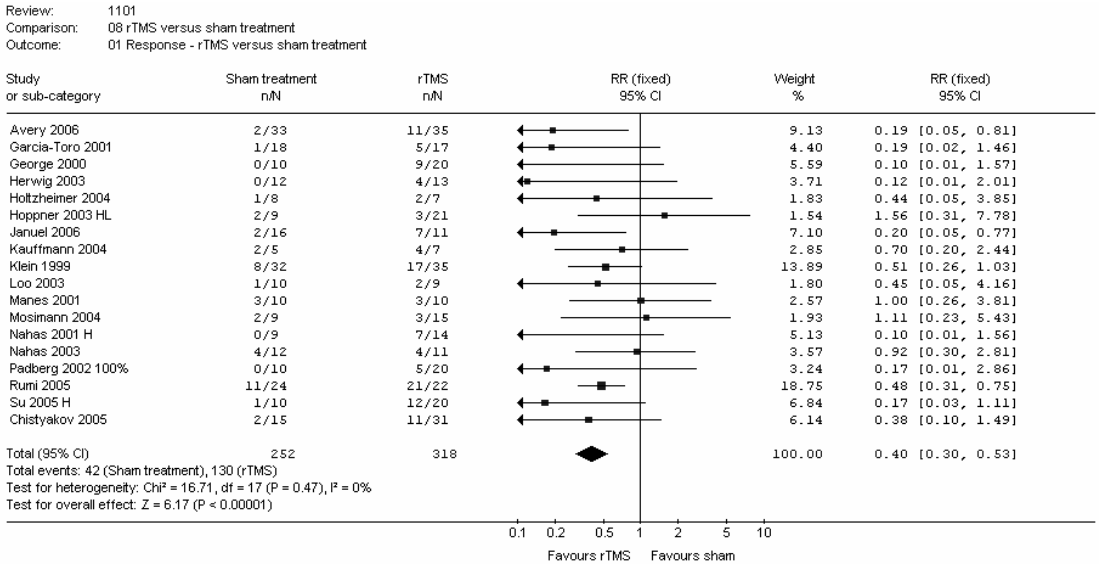
Figure 22 Studies that did not report response (rTMS versus sham) for HDRS effect size



Meta-analysis of trials with response rate as an outcome

Eighteen studies which used response rate as an outcome were investigated. The meta-analysis for this outcome is shown in Figure 23. The relative risk for the response rate, where mentioned, was 0.4 CI (0.30, 0.53) in favour of rTMS treatment over sham.

Figure 23 Repetitive transcranial magnetic stimulation versus sham – response, where reported, all studies



Response with or without anti-depressant medication

Studies were analysed according to whether patients continued with medication, or were removed from medication, during the time of the trial. This was in order to determine whether response rate of rTMS compared with sham treatment varied when patients were taking, or removed from, anti-depressant medication. Six studies reporting response rates as an outcome and in which patients had been removed from anti-depressant medication during the rTMS trial were identified (Figure 24). In comparison, 12 studies were identified in which the participants were stated to have remained on anti-depressant medication throughout the trial (Figure 25).

Meta-analysis shows that for patients who had been removed from medication for the trial relative risk is 0.26 CI (0.13, 0.54) (Figure 24). Relative risk for patients who had remained on medication throughout the trial (ie rTMS was an add-on to medication) is 0.44 CI (0.32, 0.61) (Figure 25).

Figure 24 Response without medication

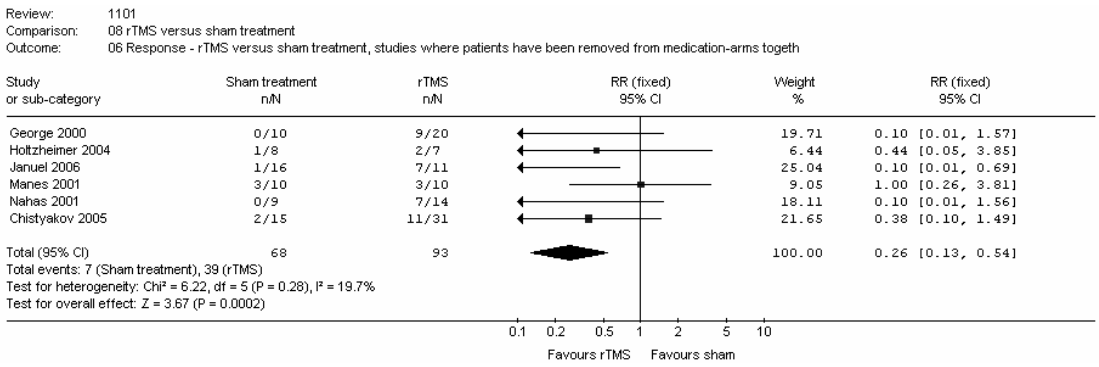
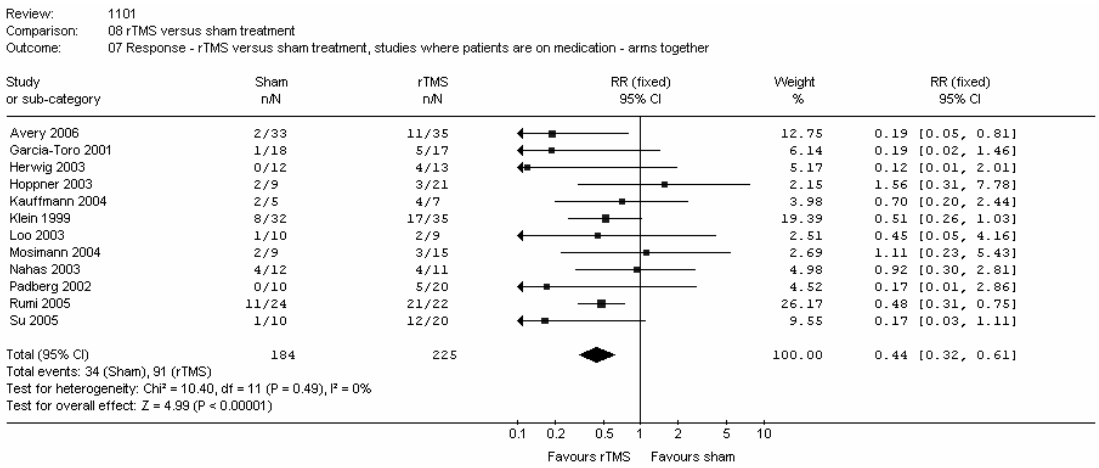


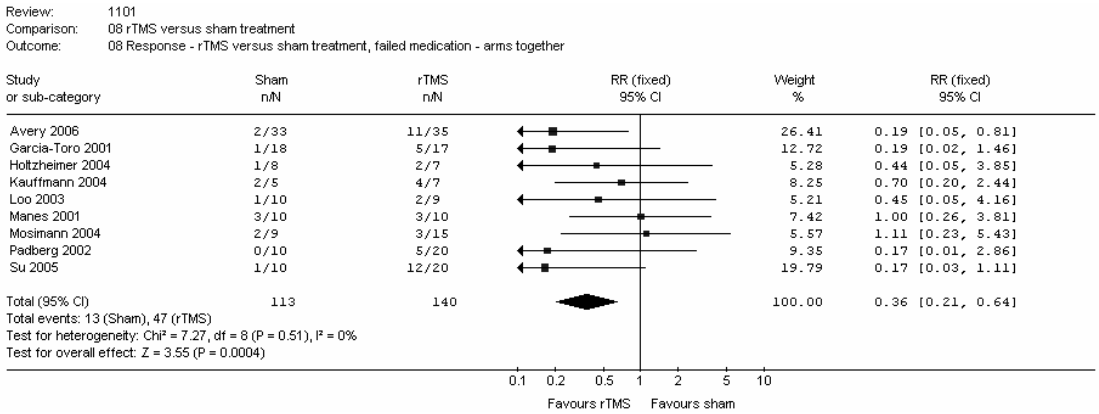
Figure 25 Response with medication



Response in patients who were medication-resistant

Studies which reported response as an outcome were investigated depending on whether the participants were stated to be medication-resistant. The definition for medication-resistance varied, but was commonly stated to be a failure to respond to two or more anti-depressants during the past month. Figure 26 shows the results of studies carried out for patients who were stated to be medication-resistant. Relative risk for these studies is 0.36 CI (0.21, 0.64); that is, rTMS was less effective in treating depression in patients who were stated to be medication-resistant. Treatment effect for sham and rTMS was reduced (11.5% and 33.6% respectively) compared to treatment effect for total studies (Figure 23, 16.7% and 40.9% respectively).

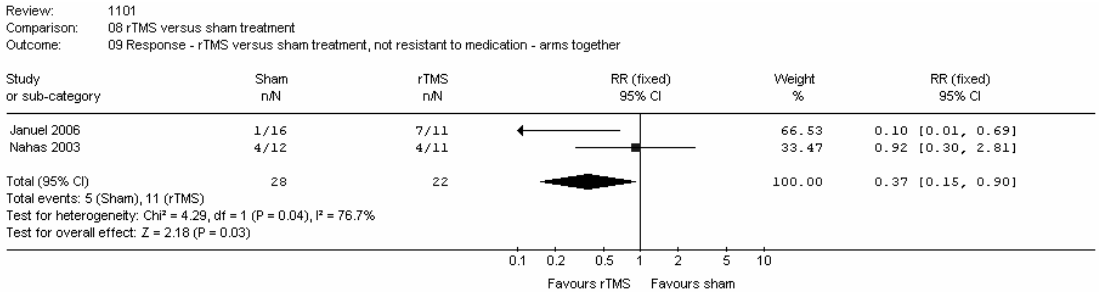
Figure 26 Response for those studies which have only included patients who are stated to be medication-resistant



Response in patients who were not medication-resistant

There were only two studies which reported response for patients who were stated to be not medication-resistant. One of these (Nahas 2003) included only bipolar patients. The result of the meta-analysis is shown in Figure 27. The remaining seven studies did not explicitly report whether or not their participants were anti-depressant medication-resistant.

Figure 27 Response for those studies which have only included patients who are stated to be not medication-resistant



Evidence from individual studies in which rTMS was either most effective, or most poor, in treating depression

Table 49 Studies which reported response rates – four studies which had the highest response rates and four studies which had the lowest response rates

	Frequency and location	Duration of treatment	Medication	Psychotic patients	Treatment-resistance
High response					
Avery 2006	10Hz LDLPFC	4 weeks	Mixed medication	Psychosis excluded	Treatment-resistant
Januel 2006	1Hz RDLPFC	4 weeks	No medication	Not excluded	Not treatment-resistant
Rumi 2005	5Hz LDLPFC	4 weeks	All patients put on amitriptyline	NR	NR
Su 2005	20Hz or 5Hz LDLPFC	2 weeks	All remained on medication	Excluded	Medication-resistant
Low response					
Hoppner 2003	20Hz LDLPFC or 1Hz RDLPFC	2 weeks	Remained on constant dosage	Not excluded	NR
Manes 2001	20Hz LDLPFC	1 week	Withdrawn from medication	Not excluded	Medication resistant
Mosimann 2004	20Hz LDLPFC	2 weeks	Remained on constant dosage	NR	Medication resistant
Nahas 2003	5Hz LDLPFC	2 weeks	2 weeks washout from psychotropic medication	Excluded	Not treatment resistant (bipolar only)

L/R DLPFC: lefr/right dorsolateral prefrontal cortex; NR: not reported

Table 49 summarises some of the main variables from a number of studies which have compared rTMS with sham treatment (where response rates were reported). See Figure 23 for the meta-analysis of these studies. Four studies were chosen in which rTMS appeared to have improved response rates over sham (Avery 2006; Januel 2006; Rumi 2005; Su 2005), and four in which rTMS and sham treatments showed equi-effectiveness, ie rTMS was least effective (Hoppner 2003; Manes 2001; Mosimann 2004; Nahas 2003). There appeared to be a great variety in treatment frequency and location of stimulation, washout from medication, inclusion of psychotic patients and inclusion of patients who were treatment-resistant. Also, Nahas 2003 included only bipolar patients in the study. The studies in which rTMS was most effective involved a longer duration of

treatment (mostly four weeks) than the studies in which rTMS was least effective (mostly two weeks). The majority of the studies had a 2-week duration; four sham studies had a 4-week duration. Two of these studies reported response as an outcome.

Comparison with published Cochrane analysis

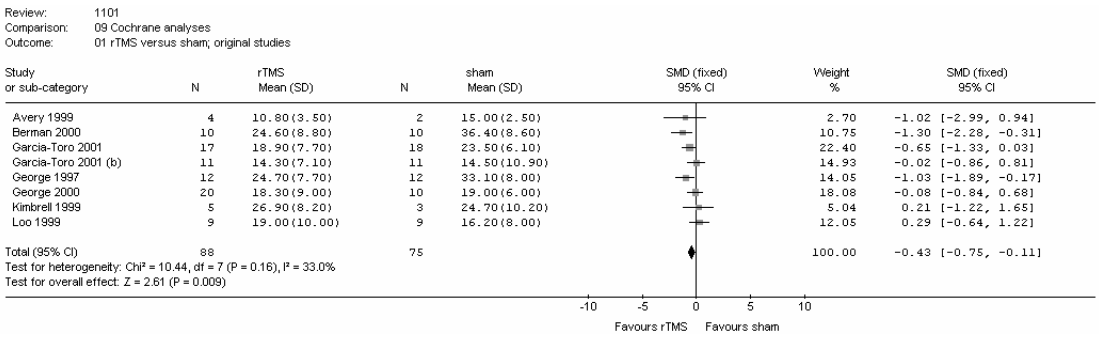
In order to confirm the validity of our results, we repeated one of the analyses carried out in Martin et al 2001, a Cochrane study of rTMS effectiveness (compared to sham, and ECT). The original analyses in Martin et al 2001 were carried out as sub-analyses according to time of outcome (1, 2 or 4 weeks), and location and frequency of treatment (eg left and high). Martin et al 2001 did not analyse response rates as outcomes, and considered the final outcome which was not corrected for baseline depression.

Original meta-analysis results for HDRS outcome 2 weeks (left, high rTMS treatment) from Martin et al 2001 was as follows:

Number of trials: 9.
Number of participants: 175.
Treatment effect: -0.35 (-0.66, -0.04).

This analysis of rTMS (left and high) versus sham for 2-week outcome was repeated with the original studies (see Figure 28).

Figure 28 Duplication of the original Cochrane meta-analysis using the original study data



Martin et al 2001 included 'Mosimann (in press)' in their meta-analysis. This study was not included in Figure 28. There was one error in the Martin 2001 analysis, namely that Loo 1999 values were baseline scores, not 2-week outcome. Baseline analyses were carried out separately in Martin 2001.

The above analysis was repeated for all studies included in this MSAC review (ie final outcome, regardless of duration of treatment). All scores were not separated where there were separate arms of rTMS treatment in a single study.

Figure 29 A repeat of the Cochrane analysis with all included studies

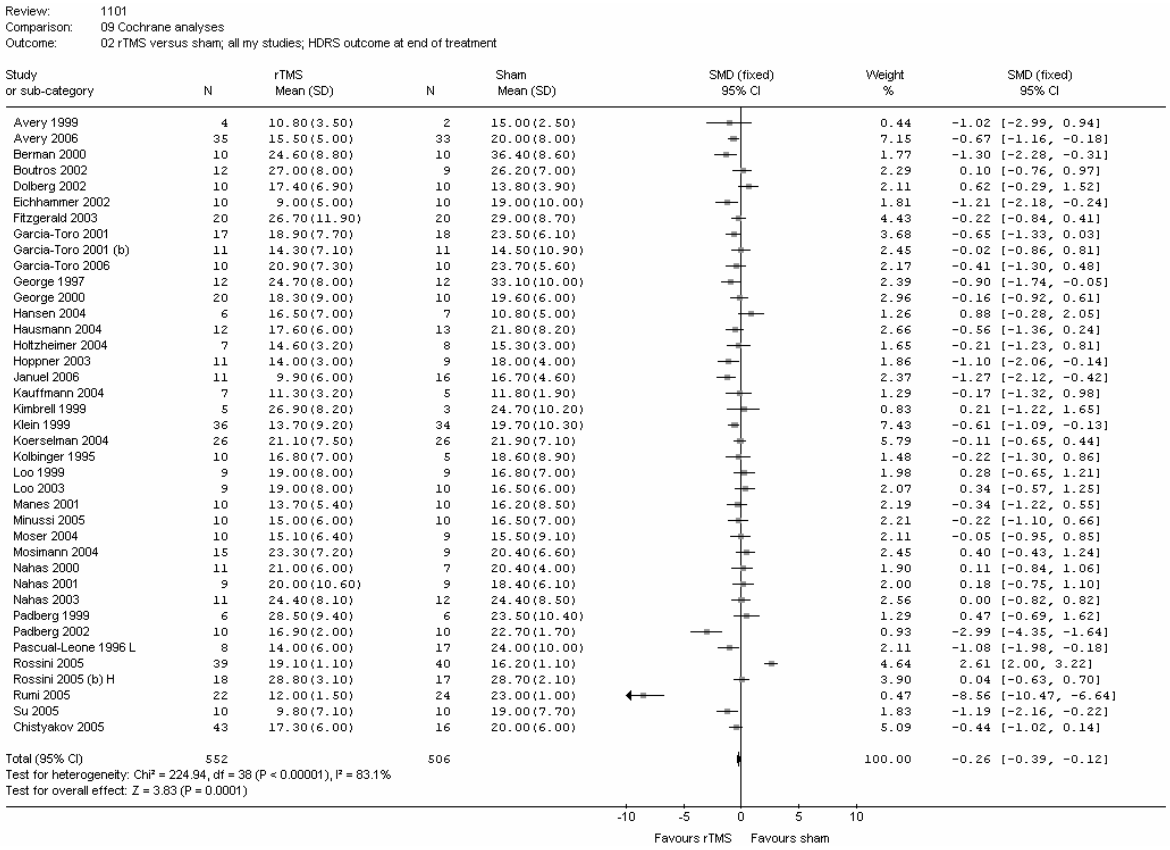


Table 50 A summary of original and duplicate Cochrane meta-analyses

Meta-analysis	Number of trials	Number of participants	Treatment effect
Original Cochrane (Martin 2001)	9	175	-0.35 (-0.66, -0.04)
Duplicate Cochrane	8	163	-0.43 (-0.75, -0.11)
Repeat of Cochrane with all available studies	39	1058	-0.26 (-0.39, -0.12)

The overall result is similar in all three analyses: rTMS is slightly more effective than and sham treatment. There is a difference in the heterogeneity of the studies included in these analyses. In Figure 27, the statistical significance of heterogeneity is p=0.16 for the original studies (with chi-squared of 10.44 and 7 degrees of freedom). Studies are much more heterogeneous in Figure 28 with the statistical significance of heterogeneity being p<0.0001 (with chi-squared of 224.95 and 38 degrees of freedom).

Effectiveness of ECT following rTMS treatment

The cost-effectiveness model of this review makes the assumption that patients who fail rTMS treatment will go on to have ECT. Kozel et al 2004 assumes that ECT is as effective for patients who have failed rTMS as it is for all patients. We searched the published literature for any studies which reported the effectiveness of ECT following rTMS treatment. The following four studies were identified:

Conca A, Hrubos W, Di Pauli J, Konig P, Hausmann A. ECT response after relapse during continuation repetitive transcranial magnetic stimulation. A case report. *European Psychiatry: the Journal of the Association of European Psychiatrists* 2004; **19**(2): 118-119.

Dannon PN and Grunhaus L. Effect of electroconvulsive therapy in repetitive transcranial magnetic stimulation non-responder MDD patients. *International Journal of Neuropsychopharmacology* 2001; **4**(3): 265-268.

Eschweiler GW, Plewnia C, Batra A, Bartels M. Does clinical response to repetitive prefrontal transcranial magnetic stimulation (rTMS) predict response to electroconvulsive therapy (ECT) in cases of major depression? *Canadian Journal of Psychiatry-Revue Canadienne de Psychiatrie* 2000; **45**(9): 845-846.

Fleischmann A, Hirshman S, Dolberg OT, Dannon PN, Grunhaus L. Chronic treatment with repetitive transcranial magnetic stimulation inhibits seizure induction in electroconvulsive shock in rats. *Biological Psychiatry* 1999; **45**(6): 759-763.

Response to ECT, following non-responsiveness to rTMS, in a single study of 17 patients was approximately 41 per cent (7/17) (Dannon & Grunhaus 2001). This compares with a response to ECT as a first-line treatment of 60.5 per cent (Table 20). Eschweiler and colleagues also investigated ECT effectiveness following a course of rTMS treatment, but did not separate patients who had responded to rTMS from those that had not responded (Eschweiler et al 2000). From their data, positive rTMS response appeared to be a positive predictor for response to ECT, whereas rTMS non-response lacked any predictive power. A case report from Conca and co-workers reported on a patient who was treated with ECT, followed by acute and maintenance rTMS, followed by maintenance ECT, each successfully (Conca et al 2004).

Therefore for the purposes of the cost-effectiveness analysis, response to ECT following non-responsiveness to rTMS will be 41 per cent (Dannon & Grunhaus 2001).

Appendix H New studies

Towards the completion of this review two new randomised controlled trials were identified which compared rTMS and ECT as treatments for severe depression. These studies were not discovered as a result of a second systematic search; therefore, it is acknowledged that there may be other published studies which were not identified subsequent to the literature search of this review (dated 8 May 2006).

The first study was a Brazilian trial which investigated the effects of rTMS and ECT in the treatment of unipolar, non-psychotic medication-refractory depression (Rosa et al 2006). Forty-two patients (mean age 43.6±10.5 years) who had undergone a 1 week wash-out of anti-depressants, anti-psychotics and mood stabilisers were randomised into each arm of the study. Each participant had a HDRS score of ≥22. There were no significant differences between each group for any baseline characteristics. Repetitive transcranial magnetic stimulation or standard ECT treatment was performed over 4 weeks. Repetitive transcranial magnetic stimulation treatment was 5 times per week to the LDLPFC at 100% MT intensity, 10Hz at 10 second trains, 25 trains per session. The total number of pulses in this study was greater than in the other studies used in the review (2,500 compared to a range of 500-1320). At baseline, 2 weeks and 4 weeks of treatment there was no significant difference between HDRS scores of patients in the ECT group and the rTMS group. With regard to the primary outcome of number of clinical responders (considered as a 50% or more decrease in HDRS score from baseline to end of treatment) there were a greater number of responders in the rTMS group (50%) than in the ECT group (40%). This difference was not significant (p=0.557). There was no significant difference between the two groups in the neuropsychological tests performance.

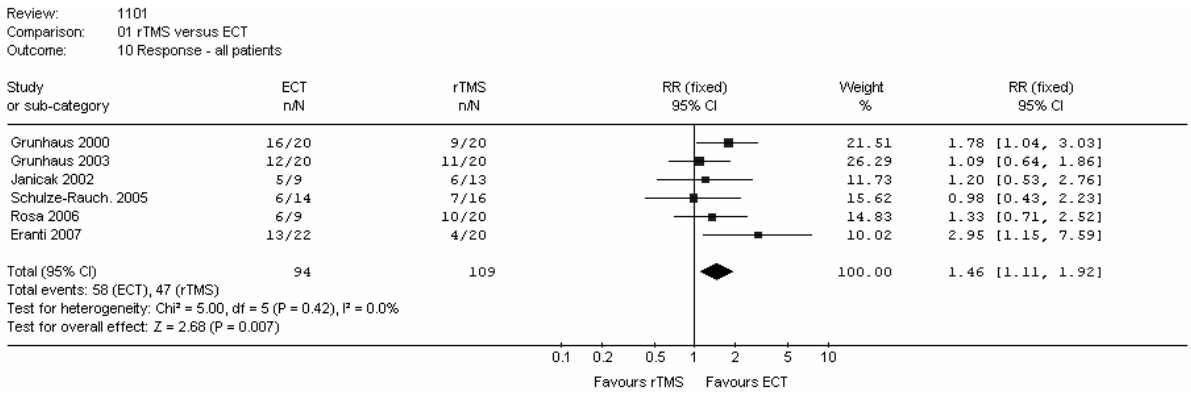
It was also considered important to highlight a second manuscript. This study (Eranti et al 2007) is the upcoming publication of the large multi-centre UK trial discussed on page 20 of this report. Forty-six patients (mean age approximately 65 years, and mean HDRS score 24) were randomised to receive rTMS or standard ECT for 15 weekdays. Participants remained on a mixture of anti-depressant medication, although no changes were made to medication during the trial. Some patients had bipolar depression (8%) and some had psychosis (15%). There were no significant differences between each group for any baseline characteristics. Repetitive transcranial magnetic stimulation treatment was to the LDLPFC at 110 per cent MT intensity, 10Hz at 5 second trains, 20 trains per session (therefore 1000 pulses per session). End-of-treatment HDRS scores were significantly lower in the ECT group compared to the rTMS group (p=0.002). There were more responders in the ECT group (59%) than in the rTMS group (17%) (p=0.006). If patients with psychosis were removed from the analysis, the percentage of responders for ECT was 59 per cent and for rTMS was 21 per cent. At six-month follow-up HDRS scores did not differ between the groups (p=0.93). Participants who had received rTMS continued to improve with regard to HDRS score, while those treated with ECT had remained approximately the same.

In summary, both of the above studies were reasonably similar to the seven included studies used in this report in terms of randomisation, participant blinding, number of participants and type and severity of depression. In addition, the length and type of rTMS treatment used were similar where reported. The result of the Brazilian study was that rTMS was slightly more effective than ECT in terms of clinical response, although this difference was not statistically significant (Rosa et al 2006). The patients in this study were reasonably young, with very well-defined depression criteria (unipolar, non-psychotic medication-refractory depression). The UK study reported rTMS to be significantly less effective than ECT in the treatment of depression after three weeks of treatment (Eranti et al 2007). The patients included were older compared with all the other studies, and had a variety of types of depression (bipolar, psychosis) and subjects remained on anti-depression medication. However, this study importantly reports the results of a 6-month follow-up, at which point rTMS and ECT depression scores remain significantly improved from baseline, and were equi-effective. Response outcomes were not reported for the 6-month follow-up.

No serious adverse events were recorded in either of these two new studies.

Both the above studies were identified through Advisory Panel communication at a date following the cut-off date for the search strategy for this review (8 May 2006). As these studies were not identified through a systematic search, it is acknowledged that other studies may have also been published in the intervening time. Bearing in mind this limitation, the potential impact of these studies on this Application was investigated. A meta-analysis of the results of these two studies, in addition to the results of the included studies, is shown in Figure 30. Taken together, the relative risk for response to treatment at the end of treatment with either rTMS or ECT is estimated to be 1.46 (95% CI 1.00, 1.70), compared with 1.28 (95% CI 0.93, 1.76) in the absence of these two new studies (Figure 2). That is, with the two new studies ECT is more effective than rTMS in treating depression (p=0.007). As can be seen in Figure 30, this is as a result of Eranti et al 2007. Although, as noted above, at 6-month follow-up Eranti et al 2007 reported that rTMS and ECT were equi-effective, the effect in both groups is unlikely to be more than natural remission as both rTMS and ECT are acute treatments the effects of which last around 1-3 months.

Figure 30 Meta-analysis of the two new studies together with the included studies showing patient response to treatment with either rTMS or ECT



In summary, it was considered that the results of the two new studies (Rosa et al 2006 and Eranti et al 2007) make minimal change to the effect size of rTMS versus ECT treatment. However, inclusion of these two studies into meta-analysis with the included studies causes ECT to be more effective than rTMS in the treatment of severe depression (p=0.007, Figure 30), compared to the previous meta-analysis (p=0.12, Figure 2). This would therefore change the overall conclusion of the review.

Appendix I Economic analysis

Overview

The four parts to this economic evaluation are:

1) a duplication of the only published economic evaluation of rTMS vs ECT;

2) a health technology assessment – cost-consequences analysis (HTA/CCA) comparing the two technologies, rTMS and ECT, for each of the groups of patients who could be provided with this treatment;

3) a cost-effectiveness analysis (CEA) and CCA comparing the two policy options specified by the Advisory Panel:

    a. no rTMS available (not subsidised as a procedure, or as part of a consultation and not practised by any hospital or other provider such as a psychologist); and

    b. rTMS available and scheduled MBS fee at applicant's proposed price;

4) an analysis of the supply side issues concerning the financial and operational feasibility of uptake of the technology by providers.

This report details each of these parts of the economic evaluation analyses in terms of:

- their rationale;
- the data and assumptions;
- methods of analysis (presented as tables which can then be reviewed on linked spreadsheets to observe the maths – unfortunately the algebra is too extensive too include more than is currently in the text of this document); and
- the results.

The key concepts and results for each of these parts are summarised below.

1) Duplication of published study using Australian estimates

The only published study of the economics of rTMS (Kozel et al 2004) compares the costs and effect (additional responders) for a cohort of patients using rTMS and a cohort using ECT. The duplication used:

- Australian figures for number of patients expected to have ECT in 2005/06 (6,212);
- Australian costs; and
- treatment effect estimates derived for this evaluation.

This first duplicated analysis is a HTA/CEA, ie a cost-effectiveness analysis of two technology options – ECT and rTMS. The results of the duplication (Table 51) suggest that the total savings to the hospital sector are significant but that there is a reduction in the number of responders. The analysis assumes that all patients who have rTMS will have it in the community and all ECT is in hospital.

Table 51 Duplication of published study using Australian data: HTA options, results

	rTMS only vs ECT only
Additional responders	-870
Additional cost to MBS	$497,512
MBS cost per additional responder	n/a
Savings to hospitals	$62,896,135
Savings total	$62,398,624

HTA: health technology assessment, MBS: Medicare benefits schedule

The published study then compares the policy of ECT only with rTMS and ECT for non-responders. This is a simple version of a policy/CEA. It compares the costs and effect of two alternative polices (or strategies) for treatment of severe to moderate treatment resistant depression (SMTRD). It assumes realistically that non-responders to rTMS may have ECT. The model assumes all non-responders to rTMS have ECT. It also assumes that the effectiveness of ECT for this group of rTMS non-responders is equivalent to the effectiveness for patients who are rTMS naïve (that is, the same as the treatment effect for ECT alone). These two assumptions lead to both the published and duplicated analysis estimating that there are additional responders and societal savings available under such a policy.

Table 52 Duplication of published study using Australian data: policy options, results

rTMS plus ECT vs ECT only	
Additional responders (1)	1,133
Additional cost to MBS (2) ($)	4,913,316
Cost to MBS per additional responder (#) ($)	4,336
Saving to hospitals (4) ($)	25,276,829
Savings total ($)	20,363,512

ECT: electroconvulsive therapy, rTMS: repetitive transcranial magnetic stimulation

The shortcomings of the published analysis as evidence to inform the MSAC decision process include that:

1. not all patients otherwise having ECT will have rTMS in the community;

2. there are multiple sites (hospital or community), sectors (public or private) and episode types (same-day, multi-day, outpatient and clinics) at which people can have ECT or rTMS, each of which has distinct resource uses associated with it;

3. not all non-responding rTMS patients will have ECT second line;

4. if a non-responder to rTMS has ECT, it is unlikely there will be additional responders in this cohort over and above what would have happened had they had ECT alone; and

5. rTMS will also be provided to SMTRD patients who would otherwise not have ECT, and are either hospitalised or in the community.

2) CCA and partial CEA of technologies

Part II of the economic evaluation expands the simple economic evaluation to take into account most of the points raised in relation to the limitations of a simple CEA. Its objective is to identify the costs and consequences of each possible combination of site, sector, type of care and patients, with and without rTMS being available. It provides the evidence that can inform the decision: 'for which group of patients and at which site should the MBS subsidy for rTMS be provided?' It also is the main input into the CEA/CCA of the policy options.

The four coded groups of patients identified as part of the evaluation are presented in Table 53.

Table 53 The four patient groups

Patient group	SMTRD Patients who are moderate or severely depressed and refractory to at least two courses of pharmacotherapy.
oE(y)oH(n)	Would otherwise have ECT (oE(y)) and been hospitalised but if had rTMS, would be able to have it in the community setting (oH(n)).
oE(n)oH(n)	Would NOT otherwise have ECT (oE(n)) and not hospitalised (oH(n)) and if had rTMS, would be able to have it in the community setting.
oE(y)oH(y)	Would otherwise have ECT (oE(y)) and been hospitalised but if had rTMS, would NOT be able to have it in the community setting and would remain in hospital (oH(y)).
oE(n)oH(y)	Would NOT otherwise have ECT (oE(n)) but require hospitalisation and if had rTMS, would NOT be able to have it in the community setting and would remain in hospital (oH(y)).

ECT: electroconvulsive therapy, oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no), rTMS: repetitive transcranial magnetic stimulation, SMTRD: severely or moderately depressed treatment resistant

These patients can be treated in a number of sites and five combinations of patients and sites and admission types were identified and included. For this analysis it is assumed that all admitted patients are treated at a private hospital and the only costs considered are MBS. It is also assumed that all non-responders to rTMS have ECT if they would otherwise have had ECT. The summary presented in Table 54 quantifies the common sense result that the greatest gains in resource use are for patients who are able to have rTMS treatment in the community rather than ECT as same-day or multi-day patients. There is no change in number of responders in this cohort due to the following two assumptions: 1) the maximum response rate for the cohorts who have rTMS plus ECT for non-responders is the response rate for ECT alone for this cohort (no additional responders) and 2) all patients who fail to respond to rTMS have ECT second line (no foregone responders). The additional responders are only possible in the patients who would otherwise not have had ECT – either already hospitalised (within restriction) or outside restriction (in community).

This HTA/CCA reports the costs and consequences and in some cases cost-effectiveness of rTMS for five separate groups of patient-site combinations. It does not combine patients from each group for an overall estimate of cost-effectiveness of the policy to subsidise rTMS through the MBS. This step, which requires estimates of the number of patients in each of these groups, is performed in the policy/CCA-CEA part of the evaluation. The HTA/CCA does identify resource use for hospitals regardless of whether public or private but the HTA/CEA does not include estimates of public hospital costs, only MBS costs of private hospitals. The reasons for this are detailed in the body of the report. The public hospital costs are considered in the policy/CCA-CEA.

Table 54 Summary of the effects on MBS costs and bed days (100 patient cohort analysis; all admissions are private)

	Change in effect		Use		Partial ICERs	
Patient group and changed procedure	Responders	Depression free months	MBS costs ($)	Bed days	Additional MBS cost ($) per additional month depression free	Additional MBS cost ($) per additional bed day
oE(y)&oH(y): ECT multi-day vs rTMS plus multi-day ECT for non responders	0	0	62,174	781	n/a	n/a
oE(y)&oH(n): ECT multi-day vs rTMS in private clinic plus multi-day ECT for non responders	0	0	62,174	-720.83	n/a	86
oE(y)&oH(n): ECT same-day vs rTMS in private clinic plus same-day ECT for non responders	0	0	62,174	-480.00	n/a	130
oE(n)&oH(y): Multi-day admission no ECT vs rTMS in multi-day admission	33	99	65,094	0.00	658	n/a
oE(n)&oH(n): Otherwise in community and no ECT	33	99	106,350	0	1,074	n/a

ECT: electroconvulsive therapy, ICERs: incremental cost effectiveness, MBS: Medicare benefits schedule, , oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no), rTMS: repetitive transcranial magnetic stimulation

3) Cost-effectiveness: cost consequence of policy options

The objective of the policy/CEA and policy/CCA is to evaluate the policy comparison identified by the Advisory Panel, viz:

1. no rTMS available; and

2. rTMS available at hospitals and private psychiatrist consulting rooms and rTMS performed at private hospitals or rooms by psychiatrists will be subsidised at the applicant's nominated scheduled fee of $150.

The policy/CCA and policy/CEA has three primary steps beyond the HTA/CCA.

1. Estimate the number of patients in each of the four groups (Table 55), and the number of these patients whose care, in the absence of rTMS, would occur in each of the possible sites and sectors.

2. Estimate the number of patients in each group-site combination who would have rTMS by predicting referral patterns, and the number of non-responders who would have follow-up ECT.

3. Identify the full resourcing and financing implications for public hospitals and MBS, for each of the possible combinations of sites with and without rTMS available.

For example, how many of the 2,619 patients who would otherwise have ECT but would not otherwise require to be hospitalised (oE(y)oH(n)) were in private hospitals? Of these, how many would have been multi-day admissions? Of these how many would have rTMS if it were available? Of these, how many would have rTMS at private clinics? If they failed rTMS, what proportion would have follow-up ECT? What would be the resource use associated with these patients under the two courses of care?

Table 55 Estimate of the total number of patients in each of the four groups

	oH(y)	oH(n)	Total
oE(n)	19,162	174,626	193,788
oE(y)	3,593	2,619	6,212
Total	22,755	177,245	200,00

oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no)

The results, summarised in Table 56, indicate that there will be around 268,000 rTMS procedures in the first year but a reduction in ECTs of only 28,000. The primary reasons for this are: 1) Some of the two groups of SMTRD patients who would otherwise not have ECT will have rTMS and represent additional procedures; and 2) around half of the 60% of patients who would otherwise have had ECT and do not respond to rTMS are expected to have ECT as second line. Also, the net gain in responders hides the loss in responders for the oE(y) groups.

The analysis suggests that there will be an average additional cost per additional month of response for the policy of subsidy compared to the policy of no availability of rTMS of $746 per additional month depression-free.

Table 56 Summary of results

Unit	All patients
Procedures	
ECT	-30,355
rTMS	268,974
Responders	
Loss	-287
Additional	6,043
Net	5,756
Activity	
Multi-day seps.	-103
Bed days	-1,548
Same-day	-10,414
Outpatient clinics	27,078
MBS consultations (39)	79,510
Resources	
Health professional hours	74,618
Tests	-6,071
Financing ($M)	
MBS ($M) (40)	12.87
State ($M)	-1.34
PHI ($M)	-0.30
Total ($M)	11.24
ICER: $ per additional responder	1,952

ECT: electroconvulsive therapy, MBS: Medicare benefits schedule, Mutti-day seps.: multi-day separations, OP clinics: out patient clinics,PHI: private health insurers, rTMS: repetitive transcranial magnetic stimulation,

4) Supply side issues

The policy/CCA and policy/CEA in Part IV of the evaluation implicitly assume that the expected patterns of referral by psychiatrists will be met by the providers of rTMS. That is, if a patient is referred, they will be treated as referred. If the demand is not met as expected, for example if there is limited provision by public hospital outpatients, then this will impact on the overall cost-effectiveness of the proposed policy compared to the non-availability of rTMS. This impact occurs for three reasons. First, if the number of services that can be supplied meets the demand, but the sites at which these services is provided differs from expected referrals, then both the total costs to the MBS and public hospitals and the cost effectiveness will change from what is expected. The number of additional responders will not change. Second, if the capacity and incentive to supply rTMS services in the private sector is greater than the expected referral patterns, then there is an incentive, particularly due to fixed capital costs, to increase activity in the oE(n)oH(n) group of patients (Table 53). Third, if the number of patients referred is beyond the number of services that suppliers are willing to supply under proposed incentives, there may be targeted rationing that changes the mix of patients who have rTMS and hence both the additional cost and additional effect.

Evidence of the economics of the supply of rTMS services is as crucial as the evidence of the economics of demand for rTMS in informing the decision to subsidise rTMS. An extensive analysis of the possible scenarios for supply and demand is beyond the time frame of this evaluation. A series of small analyses were performed to address the question of incentive and capacity to supply rTMS services under a range of options for the scheduled fee for rTMS (no subsidy, opportunity cost subsidy (the value of the time taken to perform the procedure), referenced subsidy (referenced to the ECT subsidy) or applicants fee).

The results of one of these analyses are presented in Table 57. An expected 8,686 patients would be referred to rTMS at private clinics. If these clinics operate at near maximum capacity, they will see 197 patients a year. Forty-five machines could be supported in the private sector (outside hospitals) nationally if all operated at near maximum capacity. This would represent a $1.7M market for rTMS machines in the private clinic sector. At a patient co-payment of $30 per session or $360 per course, and at the suggested scheduled fee of $150, the surplus to clinics nationally would be $9.3M, which is the additional income nationally after the opportunity cost of foregone consultations and additional costs of four year loan repayment are removed from the additional revenue.

Table 57 Number of sites that can be supported with expected private clinic patients

Nominated ARPF per session (58)	$20	$30
ARPF per course (59)	$240	$360
Sites supporting expected private clinic patients, at maximum capacity (60)		
Expected patients (41)	8,686	8,686
Maximum patients per site (capacity adjusted) (41)	197	197
Sites supporting expected patients-sites operating at maximum capacity (61)	44	44
Size of market for machines in private sector at maximum capacity (62)	$1,767,122	$1,767,122
National surplus above consulting only clinic at maximum capacity (adj) and nominated ARPF and maximum sites (63)		
Policy 1 (42)	-$5,263,621	-$4,221,330
Policy 2 (43)	$1,505,018	$2,547,309
Policy 3 (44)	$246,972	$1,289,264
Policy 4 (45)	$8,025,592	$9,067,883

ARPF: above rebate patient fee

Part I Duplication of the published economic evaluation of rTMS vs ECT

Summary of Part I:

Primary objectives:

- to reproduce the published economic evaluation of rTMS vs ECT using Australian costs and evaluation-specific treatment effects and baseline response rates.

Analyses performed:

- a HTA/CEA of ECT vs rTMS for patients would otherwise have ECT
- a policy/CEA of ECT vs rTMS with ECT for non-responders to rTMS
- private hospital ECT only.

Analysed considered but not performed:

- extension from acute treatment to maintenance treatment, as per published evaluation (not performed because subsidy is proposed for acute treatment only)
- public hospital version (not performed because of limitations of published analysis).

Results:

- for rTMS only vs ECT, 1,133 less responders (a 30% reduction) and savings of around $62 to health system, mainly due to reduced bed days
- for rTMS plus ECT vs ECT, no loss in responders and savings of around $20M to health system, mainly due to reduced bed days.

How analysis informs subsequent analyses for this evaluation:

- provides five indicators for the development of further analyses.

Caveats:

- simple costing used in duplication
- model makes two assumptions that ensure there is no loss in responders under policy, but these assumptions are not supported by evidence and are not conservative
- assumptions regarding the cumulative effect of rTMS plus ECT for non-responders
- assumptions regarding all non-responders to having second line ECT.

The four objectives of Part I are:

1) to present a simple reproduction in an Australian setting, of the only published evaluation of rTMS (Kozel et al 2004);

2) to illustrate the issues concerning the difference in the cost-effectiveness of alternative health technologies, the clinical decision, and the cost-effectiveness of the policy decision (the decision to subsidise) as they pertain to the proposed rTMS listing;

3) to identify some of the shortcomings of the published evaluation, in both the context of Australian health system and more generally, hence identifying a path forward for this MSAC evaluation; and

4) to perform a calibration[11] function for the remaining simulations.

A literature review was performed and one economic evaluation of rTMS vs ECT was found (Kozel et al 2004). It is a cost-effectiveness analysis comparing the cost per additional responder of using rTMS only, ECT only or rTMS followed by ECT for non-responders.

The maintenance arms were not included in the simple analysis and the treatment effects from the meta-analysis performed for this evaluation were used. The number of ECT procedures is for the Australian population (see Table 76). The simple HTA/CEA illustrates the results of the meta-analyses, namely that there would be less responders if these patients had rTMS rather than ECT.

Table 58 Duplication of published study: HTA options

rTMS only		ECT only	
rTMS treatment		ECT treatment	
6,212		6,212	
responders	non-responders	responders	non-responders
48%	52%	62%	38%
2,982	3,230	3,852	2,361

ECT: electroconvulsive therapy, HTA: health technology assessment, rTMS: repetitive transcranial magnetic stimulation

The proposed MBS rebate for rTMS and other MBS costs were included. Private hospital costs were taken very simply as the cost of a public hospital bed day cost for a depressed patient, less the ECT component (see Table 81 for derivations). For the purpose of this analysis this detail is sufficient to show the main cost advantages of treating patients with rTMS rather than ECT.

[11] A calibration allows formal comparison of a simple or published model with the proposed model. The parameters of the proposed model are set to simulate the reference model and any differences in the results are explained.

Table 59 Duplication of published study: simple costs

ESTIMATES	rTMS	ECT
MBS rebate		
Per treatment	$128	$156
Psychiatrist	$128	$62
Anaesthetist	$0	$94
Number of sessions	12	10
Tests	$0	$47
Per initial consultation	$65	$65
Per course	$1,595	$1,675
Hospital cost (prelim estimate)	$0	$10,125
Per day	$0	$506
Days	0	20
Total per course	$1,595	$11,800

ECT: electroconvulsive therapy, MBA: Medicare benefits schedule, rTMS: repetitive transcranial magnetic stimulation

The results of the HTA/CEA are presented in Table 60 and Table 61. The savings in bed day costs to the hospitals is in the order of $62M per year but the additional costs to the MBS would be small because the additional costs of the rTMS rebate would be offset by the savings in anaesthetist costs. This analysis has limitations. Not all of these patients are in the private sector and many ECT patients are same-day, not multi-day.

Table 60 Duplication of published study: HTA analysis

ESTIMATES	rTMS only	ECT only
Responders	2,982	3,852
Treatments		
ECT Treatments	NA	6,212
rTMS Treatments	6,212	NA
MBS cost	$9,907,927	$10,405,438
Hospital cost	$0	$62,896,135
Total costs	$9,907,927	$73,301,574

ECT: electroconvulsive therapy, HTA: health technology assessment, MBA: Medicare benefits schedule, rTMS: repetitive transcranial magnetic stimulation

Table 61 Duplication of published study using Australian data: HTA results

	rTMS only vs ECT only
Additional responders	-870
Additional cost to MBS	$497,512
MBS cost per additional responder	n/a
Savings to hospitals	$62,896,135
Savings total	$62,398,624

ECT: electroconvulsive therapy, HTA: health technology assessment, MBA: Medicare benefits schedule, rTMS: repetitive transcranial magnetic stimulation

The published study also reviewed the policy option that ECT would be available for patients who are non-responders to rTMS. These patients who had second-

line ECT were assumed to have the same response rate to ECT for all patients, regardless of whether they were responders to rTMS (Table 62). For this reason, in the published study there will be additional responders for rTMS followed by ECT for non-responders, compared to ECT alone (Table 63). This result is not consistent with what would be expected on clinical grounds, and it is essential that the simulation produced for this evaluation corrects for this.

Table 62 Duplication of published study: policy options

rTMS only		ECT only		rTMS and ECT for non-responders	
rTMS treatment		ECT treatment		rTMS treatment	
6,212		6,212		6,212	
responders	non-responders	responders	non-responders	responders	non-responders
48%	52%	62%	38%	48%	52%
2,982	3,230	3,852	2,361	2,982	3,230
				ECT treatment	
				responders	non-responders
				62%	38%
				2,003	1,228

ECT: electroconvulsive therapy, rTMS: repetitive transcranial magnetic stimulation

Table 63 Duplication of published study: policy options and analysis

ESTIMATES	rTMS only	ECT only	rTMS and ECT for non-responders
Responders	2,982	3,852	4,985
Treatments			
ECT Treatments	0	6,212	3,230
rTMS Treatments	6,212	0	6,212
MBS cost	$9,907,927	$10,405,438	$15,318,755
Hospital cost	0	$62,896,135	$32,705,990
Total cost	$9,907,927	$73,301,574	$48,024,745

ECT: electroconvulsive therapy, MBA: Medicare benefits schedule, rTMS: repetitive transcranial magnetic stimulation

From the duplication it appears that even though the additional costs to MBS are higher than for rTMS alone due to the additional ECT procedures, the cost to the MBS of an additional responder is around $4,336 and the savings in hospital bed days are in the order of $20 (Table 64).

Table 64 Duplication of published study using Australian data: policy options and results

rTMS plus ECT vs ECT only	
Additional responders (1)	1,133
Additional cost to MBS (2) ($)	4,913,316
Cost to MBS per additional responder (3) ($)	4,336
Savings to hospitals (4) ($)	25,276,829
Savings total ($)	20,363,512

ECT: electroconvulsive therapy, MBA: Medicare benefits schedule, rTMS: repetitive transcranial magnetic stimulation

How the duplication of the published analysis informs the direction of the evaluation

The published approach to the analysis of the economics of rTMS would be broadly consistent with MSAC guidelines, if accompanied by a sensitivity analysis, more accurate costing and allocation of current costs across private and public sector hospitals. The analysis is of the standard health technology cost-effectiveness analysis (HTA/CEA) form and compares the cost and effect of using rTMS for the target group of patients, namely those who would otherwise have ECT and are refractory to pharmaco-therapy. A whole of system approach to the economic evaluation of policy options was adopted. As this evaluation progressed, a number of issues that would not have been apparent had a cohort only approach been used were raised and incorporated in the analysis. The main issues are summarised below.

1) Effectiveness of ECT for non-responders to rTMS

The published analysis assumed that the response rate to ECT for people who are non-responders to rTMS is the same as the response rate for patients who have ECT only. This is the source of the additional responders that the analysis indicates. There is no evidence to assume that this is the case. In fact the response rate to ECT may act as a 'ceiling' to the overall cumulative response rate for the cohort.

2) Effectiveness of rTMS compared to ECT

If the evidence supported the position of the published economic evaluation, namely that to introduce rTMS into the treatment algorithm results in improved patient outcomes, then a standard CEA for this group would be feasible. This position is not supported by any evidence and is unlikely to have clinical support. More importantly, for a cohort of patients having rTMS followed by ECT for non responders, the probability of response is lowered because there are patients who will choose not to have ECT following non-response to rTMS. The proposed change in treatment algorithm is likely to reduce the number of depression free months for a cohort of patients who would otherwise have ECT alone.

It is conventional to argue that if a new technology is less effective than an existing technology, then an economic evaluation will not be performed; however, choice of therapy is not based on comparative effectiveness alone. In the case of ECT, some patients will be willing to forego effectiveness to avoid having a general anaesthetic. Patients and clinicians will consider rTMS and rTMS plus ECT for non-responders, despite this algorithm resulting in a reduced effect in terms of depression-free months. The CEA of a less effective but preferable technology that is also cheaper requires a number of adaptations to standard methods, for example, the calculation of an ICER.

3) Patients – four (not one) groups

Four groups of patients, who may have rTMS if it is available through the MBS, were identified (Table 65). The resource implications and/or clinical implications for each of these groups of patients differ and they were analysed separately.

While predicting uptake amongst three of these groups is relatively straightforward to estimate, the uptake amongst the second and largest group is more difficult to predict. In addition, this group is outside the strict interpretation of the proposed listing for the procedure.

4) Effectiveness of rTMS for treatment resistant severely depressed who will not have ECT

The meta-analysis of ECT vs rTMS was relevant for two (1 and 3) of the four groups of patients (see Table 65). An additional meta-analysis was performed of rTMS vs Sham (with or without pharmaco-therapy) to inform the treatment effect for the remaining two groups of patients.

5) Bed days

Bed days in public and private psychiatric wards and hospitals are unlikely to be best treated as a financial savings to the sector. They have value to the system so it is preferable to treat it as a consequence and consider the cost per bed day made available as an indicator. This is particularly important as the overall effect for patients who would otherwise have ECT in terms of responders is likely to be worse than ECT alone due to the attrition rate for follow-up up ECT.

Part II CCA and CEA of HTA for each patient group and site

Summary of Part II

Primary objectives:

- to estimate the costs and consequences and the ICER for each group of patients who could have the procedure;
- to adapt the treatment effect used in the published analysis to more accurately reflect the combined effect of rTMS and ECT for non-responders to ECT.

Analyses performed:

- CEA and CCA of five different ways in which current care could be replaced by rTMS, using staff hours, tests and bed days (CCA) and MBS costs (CEA).

Analysed considered but not performed:

- a CEA of public hospital costs (resource only addressed but no CEA from the public hospital perspective performed).

Results:

- The summary indicator varies depending upon whether the outcome is additional responders or bed days freed.

Caveats:

- These results assume that all non-responders to rTMS go on to have ECT and all hospital care is private.

Patient groups and sites

All patients referred to in this report have severe or moderate treatment resistant depression (SMTRD).

There are two ways to further classify these patients: whether they would require hospitalisation if they had rTMS (despite rTMS not requiring a GA) and whether they would otherwise (in absence of rTMS) have had ECT. This leads to four groups of patients, as follows (Table 65):

1) oE(y) oH(y) – patients who would otherwise have ECT and are hospitalised for a range of factors – would require hospitalisation even if no ECT;

2) oE(n) oH(y) – patients who would otherwise NOT have ECT (eg non-tolerance of GA), but are hospitalised for their depression;

3) oE(y) oH(n)– patients who would otherwise have ECT as same-day or greater than one day admitted patient, but who would not need to be admitted if had rTMS;

4) oE(n) oH(n) – SMTRD patients who would otherwise NOT have ECT but are not hospitalised for their depression.

The characteristics and core benefits and costs of providing rTMS to each of these four groups are outlined in the summary table (Table 65). Groups 1, 3 and 4 are within the proposed listing but some patients in group 2, the largest group, are likely to be included in actual practice.

Table 65 Four groups of patients: characteristics

	oH(y)	oH(n)
oE(n)	1. Patients hospitalised for depression and other issues, who would not otherwise have ECT. Some exclusion criteria will be shared between ECT and rTMS but others, such as tolerance of GA, are not. If these patients have rTMS, will not leave the hospital for treatment but may be responders and hence be discharged earlier than otherwise. Benefits: Additional depression free months No bed days gained. Costs: Additional MBS rebate and patient co-payment (if private provider) Additional cost to public hospital.	2. Patients who are not hospitalised for their depression or any other reason and would otherwise not have ECT. Could have rTMS at clinic or as outpatient. Benefits: Additional depression free months No bed days gained. Costs: Consultations displaced Additional MBS rebate and patient co-payment (private hospital or clinic) Outpatient clinic consultations increase.
oE(y)	3. Patients who are hospitalised for depression and other issues and would otherwise have ECT. If have rTMS, they will remain in hospital. If they are non-responders to rTMS and have ECT as follow up will have second admission or expended stay. May have ECT if non-responders to rTMS. Benefits: Some patients have preference for rTMS. Costs: Additional bed days or admissions for non-responders to rTMS who have follow up ECT Loss in responders if less than 100% follow-up Additional MBS rebate and patient co-payment (private hospital).	4. Patients who are admitted (same day or >1 day) for ECT, but if have rTMS, will have it as outpatient or private clinic. Benefits: Bed days gained. Costs: Loss in responders if less than 100% follow-up Additional MBS rebate and patient co-payment (private hospital or clinic).

ECT: electroconvulsive therapy, GA: general anesthetic, MBA: Medicare benefits schedule, oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no), rTMS: repetitive transcranial magnetic stimulation

Sites and providers: options

The objective of this section is to identify the combinations of sites and providers at which it is possible under existing TGA legislation to provide rTMS.

The financial and operational viability of providing rTMS at these sites and with these providers is considered in Table 66.

The following table summarises the site-provider combinations possible.

Table 66 Possible combinations of sites and providers consistent

	Psychiatrist	GP	Nurse	Psychologist	Clinician plus other operator
Hospital– admitted patients	✓	✓	✓	✓	✓
Hospital Outpatient clinics	✓	✓	✓	✓	✓
Psychiatrist consulting rooms	✓		✓	✓	✓
GP rooms		✓	✓	✓	✓
Psychologist rooms			✓	✓	

For the purpose of Part II of the economic evaluation, only psychiatrist rooms and private and public hospitals are considered. It is useful to note that even if rTMS is not subsidised by MBS as a procedure and the consultations during which rTMS is provided are not subsidised, it can still occur in hospitals (private and public), private medical clinics (financed through copayments) and psychologist rooms.

Resource use: staff hours, bed days and tests

The objective of the analysis presented in Table 67 is to collate the assumptions regarding resource use in a range of setting for ECT and rTMS. Only variable costs of treatment, not the fixed costs of capital, are considered in this analysis of resource use. The estimates are presented for each site at which patients could have rTMS, and for the sites where they would otherwise have their treatment. For example, for patients who do not have ECT and are hospitalised for depression, the resources used when they have rTMS are included, as are the resources they would otherwise have used, including consultations with psychiatrists. This allows for the fact that while a patient in hospital will have additional procedures and consultations due to rTMS, they may otherwise have had consultations with psychiatrists (else additional resource use due to rTMS would be overestimated). In addition, a time frame of 6 months was used to cover the period of treatment plus a 3-month follow-up period. It was also assumed that patients who are discharged from hospital will see a psychiatrist when they are back in the community. The use of antidepressants is unlikely to be impacted by the effectiveness of rTMS or ECT over the 6-month period and therefore is not included in the resource use analysis. Patients who would otherwise be taking anti-depressants are not likely to stop and those who are not will be unlikely to start. No distinction is made between private and public sector in Part II of the economic evaluation.

An important assumption concerns the way rTMS is delivered. As discussed in the previous section, there is no requirement for the psychiatrist to provide the actual treatment and it is possible that in some situations the psychiatrist may provide it alone or a model of delivery that includes an operator only could be used. This analysis assumes that the delivery involves 12.5 minutes of psychiatrist time and 30 minutes of operator time.

Table 67 Resource use; hours and tests over 6 months

Procedure	Per treatment session				Per course					Per 6 months
	Anaesthetist time	Psychiatrist	Operator	Nursing time	Psychiatrist	Tests- CXR	Test-pathology	Multi-day days	Same-days or clinic sessions	Psychiatrist cons (hours)
ECT										
Multi-day	0.25	0.1	0.25	1	0.5	1	1	15		1.5
Same-day	0.25	0.1	0.25	1	0.5	1	1		10	1.5
rTMS										
Multi-day		0.25	0.5		0.5			15		1.5
Private clinic		0.25	0.5		0.5					1.5
Neither ECT or rTMS										
Hospital								15		6
Community										3

CXR: ?, ECT: electroconvulsive therapy, rTMS: repetitive transcranial magnetic stimulation

The inputs from Table 67 are aggregated and factored by the number of sessions per course of ECT or rTMS to provide resource use for each possible site at which rTMS and ECT can be provided (see Table 68).

Table 68 Total resource use over 6 months

Procedure	Anaesthetist time (h)	Psychiatrist time (h)	Operator (h)	Nursing time (h)	Tests-CXR	Test-pathology	Overnight (days)	Same-days
ECT								
Multi-day	2.5	3	2.5	10	1	1	15	0
Same-day	2.5	3	2.5	10	1	1	0	10
rTMS								
Multi-day	0	4.5	5	0	0	0	15	0
Clinic	0	4.5	5	0	0	0	0	0
Neither ECT or rTMS								
Hospital	0	6	0	0	0	0	15	0
Community	0	3	0	0	0	0	0	0

CXR: chest x-ray, ECT: electroconvulsive therapy, rTMS: repetitive transcranial magnetic stimulation

Treatment effect

The first objective of the analysis presented in Table 69 is to estimate the response rate for patients with ECT, with rTMS and those who have neither. The estimate of treatment effect from each meta-analysis is applied to the

population probability of response for ECT and for no therapy over a 3-month period. It was also necessary to estimate a treatment effect for ECT for people who were non-responders to rTMS. The published model (Kozel et al 2004) assumed that this was the same as the treatment effect for ECT for rTMS naïve patients, essentially creating a 'two bites of the cherry' scenario. The Advisory Panel (AP) advised that a more suitable estimate for the cumulative effect of rTMS followed by ECT for non-responders was to limit an overall response rate for the cohort equivalent to that for ECT alone. In other words, if the 52 per cent of patients who fail rTMS all have ECT then the cumulative response rate for the cohort of patients who commence rTMS is 62 per cent, the same for that of ECT alone. This assumption was modelled as an entry of 0 per cent for the base case. The important implication of this is that if some patients who fail rTMS do not have ECT as second line, then there will be responders foregone if rTMS is used as first line before ECT.

Table 69 Baseline risks and treatment effects

Baseline probability of response: after 3 months, from epidemiological studies	
Ad or no therapy	15%
ECT	62%
Treatment effect	
Average duration of effect (months)	
ECT- expert opinion	3
rTMS- no evidence of difference to ECT	3
Derived response rates	
ECT following rTMS for non responders	27%
rTMS	48%
Cumulative rTMS plus ECT for non response	62%
Basis of derivations	
Meta analysis results	
rTMS (compared to ECT from meta analysis)	0.77
rTMS (compared to anti depressants)	3.41
When applied to the baseline no therapy response rate this results in the same rTMS response rate as when the previous ratio is applied to the baseline ECT response rate	2.5
Additional response for rTMS followed by ECT compared to ECT alone (must be less than 1 less ECT response)	0%

ECT: electroconvulsive therapy, rTMS: repetitive transcranial magnetic stimulation

Table 70 summarises the response rates for each of the four groups of patients, for ECT and rTMS. For patients who would otherwise not have ECT, there is an improved response rate. The effect of creating a ceiling for the cumulative response of rTMS followed by ECT for non-responders is simulated in the model by a 27 per cent response rate for ECT for this group.

Table 70 Treatment response rates, by patient group

	Therapy	oH(y)	oH(n)
oE(n)	rTMS	38%	38%
	AD or no pharmaco-therapy	15%	15%
oE(y)	rTMS with or without AD	48%	48%
	ECT with or without AD	62%	62%
	ECT following non-response to rTMS	27%	27%

ECT: electroconvulsive therapy, MBA: Medicare benefits schedule, oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no), rTMS: repetitive transcranial magnetic stimulation

The number of sessions per course is presented in Table 71.

Table 71 Numbers of treatments per course of rTMS and ECT

Per patient	
ECT	
Courses of ECT per 6 months	1
Sessions of ECT per patient per course	10
rTMS- completed	
Courses of rTMS per 6 months	1
Sessions of rTMS per person per course	12
Consultations per course	13

ECT: electroconvulsive therapy, rTMS: repetitive transcranial magnetic stimulation

Table 72 and Table 73 summarise the results for 100 patients in each of the five cohorts simulated in this HTA/CCA. First, the change in number of hours, bed days and tests, and additional responders are presented. A partial ICER is also presented. The ICER does not aggregate the full costs and effect and so can only be considered a partial indicator of the outcome. It is assumed all patients have second line ECT if they are non-responders to rTMS, hence there are no reductions in response rate for the first three cohorts. For the first cohort there is an increase in both bed days and hours; hence the second partial estimate is not estimated. For the second, there is a reduction in both, so again it is not applicable. The MBS cost of consultations in the community and all of the rebatable services and tests identified were included. Again, it is assumed that all of the activity takes place in the private sector; however, the results of the resources-only analysis is applicable to both public and private hospitals.

Table 72 Summary of cohort analysis: resource use (all otherwise ECT or have ECT as follow-up)

		Effect		Resource use summary		Partial ICERs	
Patient group and change procedure	Procedure (post rTMS availability)	Responders	Depression free months	Staff Hours	Bed Days	Additional staff hours per additional responder	Additional staff hours per additional bed days free
oE(y)&oH(y)							
Otherwise ECT as multi-day	ECT	62	186	1,800	1,502		
Option 1- rTMS as multi-day and if ECT required, as multi-day	rTMS plus ECT for non responders	62	186	1,211	2,283		
Change		0	0	-589	781	n/a	n/a
oE(y)&oH(n)							
Otherwise ECT as multi-day	ECT	62	186	1,800	1,502		
Option 1- rTMS in clinic and if ECT required, as multi-day	rTMS plus ECT for non responders	62	186	1,211	781		
Change		0	0	-661	-781	n/a	n/a
Otherwise ECT as same-day	ECT	62	186	1,800	1,000		
Option 1- rTMS in clinic and if ECT required, as same day	rTMS plus ECT for non responders	62	186	1,211	520		
Change		0	0	-589	-480	n/a	n/a
oE(n)&oH(y)							
Otherwise Multi-day admission and no ECT	None	15	45	600	1,502		
Option 1- rTMS multi-day	rTMS only	48	144	275	1,502		
Change		33	99	-325	0	-13	
oE(n)&oH(n)							
Otherwise in community and no ECT	None	15	45	300	0		
Option 1- rTMS in clinic	rTMS only	48	144	275	0		
Change		33	99	-25	0	-1	

ECT: electroconvulsive therapy, ICERs: incremental cost effectiveness, oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no), rTMS: repetitive transcranial magnetic stimulation

Table 73 Summary of cohort analysis: MBS costs and bed days (all admissions are private, all oE(y) non-responders to rTMS have follow-up ECT)

		Effect		Summary		Partial ICERs	
Patient group and changed procedure	Procedure when rTMS available	Responders	Depression free months	MBS costs ($)	Bed days	Additional MBS cost (4) per additional month depression free	Additional MBS cost ($) per addition bed day
oE(y)&oH(y)							
Otherwise ECT as Multi-day	ECT multi-day	62	186	163,658	1,502		
	rTMS as multi-day plus ECT for non responders	62	186	225,832	2,283		
Change		0	0	62,174	781	n/a	n/a
oE(y)&oH(n)							
Otherwise ECT as multi-day	ECT multi-day	62	186	163,658	1,502		
	rTMS as clinic plus ECT for non responders	62	186	225,832	781		
Change		0	0	62,174	-721	n/a	120
Otherwise ECT as same-day	ECT same-day	60	180	163,658	1,000		
	rTMS as clinic plus ECT for non responders	60	180	225,832	520		
Change		0	0	62,174	-480	n/a	180
oE(n)&oH(y)							
Otherwise multi-day admission and no ECT	none	15	45	75,636	1,502		
Option 1- rTMS multi-day	rTMS only	48	144	140,730	1,502		
Change		33	99	65,094	0	658	n/a
oE(n)&oH(n): Otherwise in community and no ECT							
Otherwise in community and no ECT	None	15	45	34,380	0		
	rTMS only	48	144	140,730	0		
Change		33	99	106,350	0	1,074	n/a

ECT: electroconvulsive therapy, ICERs: incremental cost effectiveness, MBS: Medicare benefit schedule, oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no), rTMS: repetitive transcranial magnetic stimulation

Table 74 summarises the incremental impact of using rTMS followed by ECT for all non-responders who would otherwise use ECT. The results show that each of

the five cohorts have significantly different incremental effects and costs associated with the use of rTMS. This result guides the development of Part II of the economic evaluation, the cost-effectiveness of the policy choice.

It is crucial to perform a policy/CEA and CCA and not just a HTA/CEA or CCA, as the critical determinant of the cost effectiveness of the overall policy choice is the mix of:

- patients (oE(y), oE(n), oH(y) and oH(n))
- sector of care (public or private)
- admission type (same-day or multi-day).

Table 74 Summary of 100 patient cohort analysis for private admissions: MBS costs and bed days

	Change in effect		Use		Partial ICERS	
Patient group and changed procedure	Responders	Depression free months	MBS costs ($)	Bed days	Additional MBS cost ($) per additional month depression free	Additional MBS cost ($) per additional bed day
oE(y)&oH(y): ECT multi-day vs rTMS plus multi-day ECT for non responders	0	0	62,174	781	n/a	n/a
oE(y)&oH(n): ECT multi-day vs rTMS in private clinic plus multi-day ECT for non responders	0	0	62,174	-720.83	n/a	86
oE(y)&oH(n): ECT same day vs rTMS in private clinic plus same-day ECT for non responders	0	0	62,174	-480.00	n/a	130
oE(n)&oH(y): Multi-day admission no ECT vs rTMS in multi-day admission	33	99	65,094	0.00	658	n/a
oE(n)&oH(n):otherwise in community and no ECT	33	99	106,350	0	1,074	n/a

ECT: electroconvulsive therapy, ICERs: incremental cost-effectiveness, MBS: Medicare benefits schedule, oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no), rTMS: repetitive transcranial magnetic stimulation

Part III Policy CEA and CCA

Summary of Part III

Primary objectives:

- to estimate the cost-effectiveness of the policy alternatives:
    - rTMS is subsidised by MBS at the proposed scheduled fee of $150 and made available in public hospitals; and
    - rTMS is not available at any site and is not subsidised.

Analyses performed:

- estimate of utilisation (demand) for rTMS based on estimate of referral patterns by psychiatrists if rTMS were available and subsided by the MBS;
- a policy/CEA and CCA based on the expected utilisation and associated costs and effect;
- private and public sector costs considered.

Results:

- 22,000 rTMS procedures
- $16M per year in additional costs to MBS
- $3M in savings to the Public hospitals
- 8,000 bed days freed
- 5,600 additional responders
- $746 (MBS and public hospitals) per additional month depression free.

How informs further analysis:

- requirement for an analysis of the possible supply side constraints of meeting the expected demand

Caveats:

- additional responders
- simplified treatment of costs to public hospital
- expected demand is modelled and only approximates utilisation if the demand can be supported by providers (supply).

Background to specification of policy alternatives

The word 'policy' is used in the sense of practice (likely or actual) under the nominated regulatory structure. The use of the term is also intended to draw a distinction between the consequences (from a hospital or social perspective) of the clinical decision of procedure (rTMS or ECT) for a specific patient or cohort of homogeneous patients (an HTA/CEA, Part ii of the economic evaluation) and the decision to subsidise the procedure (policy/CEA or CCA).

In order to perform an economic evaluation of the decision to subsidise rTMS, the proposed policy of subsidy at $150 per procedure and associated consultation needs to be compared to an alternative regulatory structure. The question of 'what is the alternative to the policy of subsidy' illustrates the complexities introduced by going from HTA/CEA to policy/CEA. The important point is that these issues are explicated in policy/CEA, even if they are not resolved, whereas they are generally not addressed in the HTA/CEA.

Three policy models were identified:

1. No rTMS available in any sector or site.
2. The policy of MBS scheduled fee of $150 per procedure and associated consultation.
3. The policy of no MBS subsidy for procedure or consultation with rTMS, but rTMS provided through public hospitals, psychologists and clinicians, not only psychiatrists. Service is financed by a patient consultation fee with no MBS rebate, but possibly a private health insurance rebate.

The two options for the policy analysis were:

a) comparison between 2 and 3

b) comparison between 1 and 2.

The approach that was adopted is the second (b) above), which is consistent with MSAC practice. The evaluation is then of the availability of rTMS, with the scheduled fee of $150 compared to no rTMS, rather than the evaluation of the policy decision of subsidising rTMS through MBS (a comparison of uptake, cost and effect of rTMS with and without the MBS subsidy).

Method for policy/CEA and CCA

As can be seen from the HTA/CEA/CCA, the overall cost-effectiveness of the policy depends upon the number and type of patients who have rTMS, what they would otherwise have had, the site they have it at and how it is financed. The evaluation required estimates of the number of patients in each of the identified groups, by site. Furthermore, it was necessary to identify what proportion of these patients would have rTMS if it were available and where they would have it (as outpatients, at private clinics or multi-day, in public or private sector). The complexity of this analysis arises because each possible combination of usual care and postsubsidy care had a distinct effect and cost associated with it.

The method used in the evaluation was to first estimate the number of patients by site and type of patients who could potentially have rTMS if it were available. Estimates from the expert Advisory Panel of the referral patterns within the community and within hospitals, including second-line ECT for non-responders were elicited and modelled. Resource use (bed days, same-days, clinical sessions) and costs to public hospitals and the MBS were also estimated and modelled. This analysis of resource use was applied to the estimate of pre-rTMS and post-rTMS utilisation by site and patient type, and treatment effect. The result is a range of costs and consequences for both policy options.

This analysis was complex to formulate. Most of the steps in the analysis are presented in the following tables. The tables presenting the steps in the analysis are included to indicate the algebra behind the estimates, which is too extensive to include in the body of the report. In addition, some tables are similar, but this is because they are presenting steps in analysis not tables reporting results.

Patient numbers

Table 75 presents the estimates of the number of patients who have SMTRD in Australia, and the total number of admissions, by private and public, same-day and multi-day for this group. The sources of the 2004/05 hospital activity data are included in the associated spread sheets. SMTRD patients were assumed to be those whose principal diagnosis was either depression or recurrent depression. The evaluation estimates that there are approximately 41 admissions per 100 people with SMTRD, with many patients having more than one admission, particularly more than one same-day admission.

The current use of ECT was estimated using a number of sources of data: MBS data for private same-day and admitted, and procedure codes for same-day ECT in the public sector. Expert advice was provided that around 75 per cent of patients who were hospitalised while having ECT would have been hospitalised even if they did not have ECT. A total of 6212 patients were estimated to have ECT in 2004/05.

Table 75 Estimates of the total number of people with SMTRD in Australia and total number of admissions for this group

Adult Population	16,000,000
% of population prescribed antidepressants in one year	5.0%
Estimated number of patients treated for depression	800,000
% with treatment resistant depression- based on estimate non-response rate in clinical trials of ADs	25%
Estimated number of people per year with treatment resistant depression	200,000
Hospitalisations (2004-05) (principle diagnosis depression or recurrent depression (f33 and f 34))	
Private admissions	
Separations	
Same-day	37,875
Multi-day	11,035
Multi-day patient days	203,676
Average LOS multi-day	18
Total separations	48,910
Total days	241,551
Public admissions	
Separations	
Same-day	13,478
Multi-day	19,493
Multi-day patient days	226,705
Average LOS multi-day	12
Total separations	32,971
Total days	240,183
Total admissions	
Separations	
Same-day	51,353
Multi-day	30,528
Multi-day patient days	430,381
Total separations	81,881
Total days	481,734
Per 100 person with SMDTR	
Same-day admissions	26
Multi-day admissions	15
Total admissions	41
Days	241

AD: antidepressant, LOS: length of stay, SMTRD: severely or moderately depressed treatment resistant

Table 76 Current use of ECT in Australia

Admissions by principle diagnosis: potential ECT	
Number of separations with depressive or recurrent depressive	81,881
Same-day	51,353
Multi-day	30,528
Public hospitals- ECT	
Patients who have ECT	4,351
Same-day (derived)	1,073
Multi-day (derived)	3,278
% of all who have same-day	25%
% of multi-day who are oH(y)	75%
Number oH(y)	2,459
ECT Procedures	43,511
Same-day	10,731
Multi-day	
Multi-day (courses)	3,278
Multi-day (Procedures- derived from courses)	32,780
Private hospitals- ECT	
Patients who have ECT	1,861
Same-day	348
Multi-day	1,513
% of all who have same-day	23%
% of multi-day who are oH(y)	75%
Number who are oH(y)	1,134
Prcedures (AIHW hospital data cube)	18,077
Same-day (procedures)	3,484
Multi-day (courses)	3,270
Multi-day (Procedures- derived from courses)	31,763
Sessions per admission for ECT (derived)- one course of ECT appear to be over two admissions)	4.46
Multi-day procedures (from MBS less known same-day)	14,593
Procedures (MBS data)	
Procedures item 14224 (ECT)	18,077
Patients	1,861
Procedures or sessions per patient (derived)	9.71
Total	
Patients	6,212
Same-day	1,422
Multi-day	4,791
Otherwise comparison (OH) (if did not have ECT)	
oH	3,593
Not oH	1,198
ECT Procedures	78,758
Same- day	14,215
Multi-day	64,543

ECT: electroconvulsive therapy, MBS: Medicare benefits schedule, oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no), rTMS: repetitive transcranial magnetic stimulation

The previous two tables present the basis for and the value of the estimates of: the number of separations in which depression or recurrent depression is the principal diagnosis; the total number of ECTs performed in hospitals; and the number of patients who have ECT. Expert advice was provided that nearly all ECT would be used for people with depression, not for other conditions. It was therefore possible to combine the previous two analyses to estimate the total number of patients who are hospitalised for depression but do not have ECT. This is a group of patients who are considered candidates for rTMS, but who may not have otherwise had ECT for reasons such as unable to have a GA. The number of separations with a principle diagnosis of depression or recurrent depression are in the public domain hospital data bases. The number of patients who have these separations is not available in the public domain. The number was estimated by estimating the proportion of admitted patients who are not same-day who have ECT. Expert advice was that 25 per cent was a reasonable estimate, which suggested that depressed patients have around 1.2 admissions per year in the public and 1.5 admissions per year in the private sector. The result is an estimate of around 19,162 patients who are admitted for depression but do not have ECT for a range of reasons, compared to around 6,212 who do have ECT.

Table 77 The use of ECT in Australia amongst admitted depressed

Public	
Separations for depressed (Multi-day)	19,493
Estimated % of admitted (multi-day) depressed patients who have ECT	25%
Number of multi-day patients who have ECT	3,278
Number of admitted depressed patients who do not have ECT (derived)	13,112
Number of admitted depressed patients (derived)	16,390
Admissions per admitted depressed patients (derived)	1.19
Private	
Separations for depressed (multi-day)	11,035
Estimated % of admitted (multi-day) depressed patients who have ECT	25%
Number of multi-day patients who have ECT	1,513
Number of admitted depressed patients who do not have ECT (derived)	6,050
Number of admitted depressed patients (derived)	7,563
Admissions per admitted depressed patients (derived)	1.46
Total	
Separations for depressed (multi-day)	30,528
Number of multi-day patients who have ECT	4,791
Number of admitted depressed patients who do not have ECT (derived)	19,162
Number of admitted depressed patients (derived)	23,953
Admissions per admitted depressed patient (derived)	1.27

ECT: electroconvulsive therapy

Summaries of patients with SMTRD by characteristic and by site of care and characteristics are presented in Table 78 and Table 79. Only 2,619 of the estimated 6,212 patients who have ECT currently could have had rTMS outside the hospital setting. These are the patients for whom an analysis of the form published in Kozel et al 2004 is relevant. For the estimated 19,162 patients who are depressed and hospitalised and do not have ECT, rTMS, if it is provided, will be provided in the hospital setting, not in the community. For the 6,050 of these patients who are in private hospitals, this would represent an additional cost to the MBS. There are an estimated 174,626 SMTRD patients in the community who may or may not be using antidepressants and could be referred for rTMS. The figures in Table 78 include same day ECT as admitted patients.

Table 78 Summary of patient numbers in each of the four groups

	oH(y)	oH(n)	Total
oE(n)	19,162	174,626	193,788
oE(y)	3,593	2,619	6,212
Total	22,755	177,245	200,000

oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no)

Table 79 Summary of patient group by site of care

	oH(y)	oH(n)	Total
oE(n)			
Private hospital	6,050		
Public hospital	13,112		
Private psychiatrist or other clinician- rooms		174,626	
Total oE(n)	19,162	174,626	193,788
oE(y)			
Private hospital	1,134	727	1,861
Same-day		348 (48%)	348
Multi-day	1,134	378 (52%)	1,513
Public hospital	2,459	1,893	4,351
Same-day		1,073 (57%)	1,073
Multi-day	2,459	820 (43%)	3,278
Total oE(Y)	3,593	2,619	6,212
Total oE(Y) and oE(n)	22,755	177,245	200,000

oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no)

Public hospital costs

The costs of ECT in public hospital can be derived from the 2004/05 hospital statistics for the AR-DRGs. There is a code for ECT same-day, but none for ECT while a patient is admitted. The codes that were used to derive the estimate of costs for same-day, and for admission for depression with and without ECT are presented in Table 80.

Table 80 AR-DRG public hospital statistics for 2004/05

20405	Separations			Patient Days			Costs
	Same-day	Non same-day	Total	Same-day	Non same-day	Total	Per separation
U40Z	10,579		10,579	10,579		10,579	581
U63A	0	2,657	2,657		63,777	63,777	11,077
U63B		17,485	17,485		238,701	238,701	7,428

AR-DRG: Australian refined diagnostic related group

The estimates used in the simulation are presented in Table 82. The derivation of these estimates is presented in Table 81. It was assumed that 25 per cent of all admissions included ECT and that the additional costs of an ECT compared to other admissions in that DRG was equal to the costs of the procedure and the anaesthetist. The maths can be followed in the spread sheet. The costs of anaesthetists and psychiatrists time and the costs of additional tests were estimated using the MBS rebate (see Table 83). The operator costs are at $20 per hour. While this is not perfect, it is a useful substitute given the short time frame available for this analysis and that the focus of the evaluation is the CEA of the MBS subsidy, not a CEA for hospitals. Furthermore, there is no public domain data that allows this to be estimated any other way. With the three estimates of cost of DRG overall, additional cost of ECT compared to no ECT in admission, and the proportion of all admissions that include ECT, it was possible to derive an estimate of the cost of both ECT and non ECT admissions under these DRGs. The resource used in ECT not rTMS (tests and anaesthetists) were deducted from the cost of the admission ECT. It was assumed that the same number of bed days was required for all of these admissions. This assumption means that there is no effect on bed days of introducing rTMS to patients that would otherwise not have had ECT or changing from ECT to rTMS for other patients. The costs of rTMS in an outpatient clinic were assumed to be the same as the proposed scheduled MBS rTMS fee as there was no other basis for the estimate.

Table 81 Estimates and derivation of public hospital costs

Estimates and derivation of public hospital costs- part 1 available data				
	Multi-day bed days	Average cost per sep or course ($)	Same-days	Outpatient clinic encounters
Available data				
U60Z Mental health Treat, Same-day-ECT		551	1	
U40Z Mental Health Treat, Same day+ECT		581	1	
U63A Major Affective Disorder A>69-Cscc	24	11,077		
U63B Major Affective Disorder A<70-Cscc	14	7,428		
Estimates and derivation of public hospital costs- part 2 estimate required				
Estimates required for evaluation and derived estimates				
Multi-day ECT	15	8,830		
Multi-day no ECT	15	7,602		
Multi-day rTMS	15	7,842		
Same-day ECT		5,810	10	
Outpatient rTMS		1,800		12
Estimates and derivation of public hospital costs- part 3 derivation of estimates				
Inputs				
Weighted average of U63A and U63B	15	7,909		
Component of ECT that is not in rTMS[a]		988		
Component common to ECT and rTMS and not in U63A and U63B [b]		240		
Bed days for ECT, rTMS (same as weighted average)	15			
Same-day ECT per course		5,810	10	
Clinic sessions for rTMS outpatient				12
Derivation of ECT sep, rTMS sep and same-day rTMS and outpatient rTMS				
Cost per separation with no ECT or rTMS- adjusted weighted average of U63A and U63B [c]	15	7,602		
Base bed day cost (above divided by average days)		506		
Cost per separation with ECT (cost per sep base plus extra procedures)	15	8,830		
Cost per separation with rTMS	15	7,842		
suggested rTMS MBS scheduled fee		150		

ECT: electroconvulsive therapy, MBS: Medicare benefits schedule, rTMS: repetitive transcranial magnetic stimulation; a: MBS fee rebate used as indicator of anaesthetist and test costs; b: without ECT operator costs at $20 per session; c: assuming that 25% of seps include ECT and hence include the additional ECT cost, over and above the costs of the average non ECT admissions

Table 82 Summary of costs and increments for public hospitals over 6 months

	Multi-day bed days	Average cost ($) (ex MBS post discharge)	Same-days	Outpatient clinic encounters
Absolute costs				
Multi-day ECT	15	8,830	0	0
Multi-day no ECT	15	7,602	0	
Multi-day rTMS	15	7,842	0	0
Same-day ECT	0	5,810	10	0
Outpatient rTMS	0	1,800	0	12

ECT: electroconvulsive therapy, MBS: Medicare benefits schedule, rTMS: repetitive transcranial magnetic stimulation

Costs to MBS and private health insurers

The costs to the MBS for each of the five combinations of treatment and site for patients who have rTMS or ECT are presented in Table 83. The bottom line of the table gives the estimates of the cost to the MBS over a 6-month period and includes the costs of post-discharge consultations. The following summary table also includes the MBS costs following discharge for public hospital patients.

The cost to the private health insurers was derived using the estimates on public hospital costs and estimates of the MBS rebate. We assumed that the resources used are identical in the two sectors and without data on the differences in the financial costs. We also assumed that the total financial costs for these admissions were the same in the two sectors. We derived the costs to the PHI by deducting the MBS rebates from the costs of the admission. To estimate the costs of rTMS we used a similar process, with one exception: we added the surplus inherent in the MBS payment to psychiatrists (the additional rebate above the ECT rebate for the equivalent period of time difference in per procedure cost x the number of rTMS procedures (12)) (see Table 62).

Table 83 MBS costs over 6 months

	Private hospital including post discharge				rTMS private clinic	Post discharge (public hospital)	In community no ECT or rTMS
	ECT		rTMS	Neither			
	Same-day	Multi-day	Multi-day	Multi-day			
Anaesthetist services							
HIC items 17603 scheduled fee	$37.95	$37.95					
HIC items 20104 scheduled fee	$70.00	$70.00					
HIC items 23010 scheduled fee	$17.50	$17.50					
Rebate	75%	75%					
Scheduled fee per session	$125.45	$125.45					
Total for anaesthetist services							
MBS scheduled fee per course	$1,255	$1,255					
MBS rebate per course	$941	$941					
Psychiatrist Services							
Pertaining to rTMS or ECT treatment							
Scheduled fee per procedure (incl consultation)	$62.20	$62.20	$150.00		$150.00		
Number treatments per course	10	10	12		12		
Initial consultation per course of treatments	1	1	1		1		
Scheduled fee per course	$698	$698	$1,876		$1,876		
Rebate per course	$524	$524	$1,407		$1,407		
Other psychiatric consultations							
Number of consults (15 to 30 minutes)	3	3	3	12	3	3	6
While not admitted	3	3	3	3	3	3	6
While admitted	0	0	0	9	0	0	0
Scheduled fee per consultation	$76.40	$76.40	$76.40	$76.40	$76.40	$76.40	$76.40
Scheduled fee per course	$229.20	$229.20	$229.20	$916.80	$229.20	$229.20	$458.40
Rebate per course	$171.90	$171.90	$171.90	$756.36	$171.90	$171.90	$343.80
MBS scheduled fee per course	$928	$928	$2,106	$917	$2,106	$229	$458
MBS rebate per course	$696	$696	$1,579	$756	$1,579	$172	$344
Tests Per course, not otherwise required							
Item 58500 CHEST (lung fields) by direct radiography	$35.35	$35.35					
Item 11700 TWELVE-LEAD ELECTROCARDIOGRAPHY, tracing	$27.60	$27.60					
Scheduled fee per course	$62.95	$62.95					
Rebate per course	$47.21	$47.21					
TOTAL							
MBS psychiatrist consultations (incl procedures)	14	14	16	12	16	3	6
Total MBS scheduled fee	$2,245	$2,245	$2,106	$917	$2,106	$229	$458
Total MBS rebate	$1,684	$1,684	$1,579	$756	$1,579	$179	$344

ECT: electroconvulsive therapy, HIC: Health insurance commission, MBS: Medicare benefits schedule, rTMS: repetitive transcranial magnetic stimulation

Table 84 Private hospital costs and activity per admission or course

Admission	Resources		Financials ($)			
	Multi-day bed days	Same-day	Cost to public sector of equivalent admission	MBS rebate	PHI costs	Total costs
Multi-day						
ECT	15		8,830	1,512	7,319	8,830
rTMS	15		7,842	1,407	7,225	8,633
Cost ex MBS surplus of rTMS over ECT				617		
Surplus (additional MBS fee due to rTMS surplus)				790		
Cost incl. surplus				1,407		
No procedures	15		7,602	584	7,018	7,602
Same-day						
ECT		10	5,810		5,810	5,810

ECT: electroconvulsive therapy, MBS: Medicare benefits schedule, PHI: private health insurers, rTMS: repetitive transcranial magnetic stimulation

Table 85 Costs and resource use per patient over 6 months

	Resources				Financials ($)						
	Multi-day days	Same-day days	Out-patient clinics	MBS financed psychiatric consults (Incl procedures)	Hospital costs				MBS rebate ex hospital	Total MBS rebate	Total financial cost
					MBS	State funder	PHI	Total hospital			
Public											
Multi-day											
ECT	15			3	0	8,830	0	8,830	172	172	9,002
rTMS	15			3	0	7,842	0	7,842	172	172	8,014
No procedures	15			2	0	7,602	0	7,602	172	172	7,774
Same-day											
ECT		10		2	0	5,810	0	5,810	172	172	5,982
Outpatient											
rTMS			12	2	0	1,800	0	1,800	172	172	1,972
Private											
Multi-day											
ECT	15			14	1,512	0	7,319	8,830	172	1,684	10,514
rTMS	15			16	1,407	0	6,435	8,633	172	1,579	8,804
No Procedures	15			12	584	0	7,018	7,602	172	756	7,774
Same-day											
ECT		10		14	1,512	0	4,298	5,810	172	1,684	5,982
Private clinic											
rTMS				16	1,407	0	393	1,800	172	1,579	1,972
No procedures				6	0	0	0	0	344	344	344

ECT: electroconvulsive therapy, MBS: Medicare benefits schedule, PHI: private health insurers, rTMS: repetitive transcranial magnetic stimulation

One consideration is whether there will be an impact on the average cost per AN-DRG if rTMS is introduced. While there are savings for patients who would otherwise have ECT, there are additional costs for patients who would otherwise not have ECT. In addition, some patients who would otherwise have ECT will no longer be admitted. Using the estimates of changed mix of admitted patients (following section), we estimated the net impact on the average cost per DRG for private and public hospitals (Table 86).

Table 86 Impact of rTMS on AR-DGR costs weights

ECT Treatment Only							
	Public hospital			Private hospital			
	% of all admissions in ARDRG	Cost of admission	Est. state financial cost of admission	% of all admissions in ARDRG	Cost of admission	MBS financial cost of admission	Est. min PHI financial cost of admission
ARDRG 63A and 63B							
ECT	16%	$8,830	$8,830	16%	$8,830	$1,512	$7,319
NO ECT	84%	$7,602	$7,602	84%	$7,602	$584	$7,018
Average cost		$7,796	$7,796		$7,796	$731	$7,065
ECT Treatment with rTMS							
ARDRG 63A and 63B	% of all admissions in ARDRG	Cost of admission	Est. state financial cost of admission	% of all admissions in ARDRG	Cost of admission	MBS financial cost of admission	Est. min PHI financial cost of admission
ECT	8%	$8,830	$8,830	8%	$8,830	$1,512	$7,319
rTMS	50%	$7,842	$7,842	50%	$8,633	$1,407	$7,225
No rTMS or ECT	42%	$7,602	$7,602	42%	$7,602	$584	$7,018
Average cost		$7,819	$7,819		$8,214	$1,069	$7,145

ARDRG: Australian refined diagnostic related group, MBS: Medicare benefits schedule, PHI: private health insurers, ECT: electroconvulsive therapy, rTMS: repetitive transcranial magnetic stimulation

Referral patterns and utilisation of rTMS

Table 87 presents the policy options and comparator used in the overall economic evaluation. The evaluation for the specified policy choice is represented in this table as the base policy and policy 4. The three other options are considered only in the final analysis of supply side issues, but are included in this table as it is the only table in the model in which policy options can be specified. The preferences that are modelled in the policy analysis assume that all demand (referrals) is met by the providers of services. The analysis of referrals becomes an analysis of utilisation under policy 4.

Table 87 Policy options and base for comparisons

	Reference Rebate ($)		Scheduled fee ($)
	Hospital	Rooms	
Base for comparisons- No rTMS available	0	0	0
1. Rebate does not apply to consultation or procedure (Policy 1) No MBS rebate for consultation that includes rTMS or for rTMS as a procedure (Provision of rTMS occurs outside MBS subsided activity by public hospitals, GPs (patient co-pay), psychiatrists (patient co-pay), psychologists etc.)	0	0	0
2. Rebate is opportunity cost of time (Policy 2) MBS rebate for consultation and procedure, at 15 to 30 minute consultation OR can be alternative	57.30	64.94	76.40
3. Rebate referenced to ECT (Policy 3) MBS rebate for procedure and consultation item 14224 at 100% of ECT procedure and consultation scheduled fee	46.65	52.87	62.20
4. Rebate is at applicants proposed fee (Policy 4) MBS scheduled fee for consultation and procedure at $150 (or can be changed to any other fee)	112.50	127.50	150.00

ECT: electroconvulsive therapy, MBS: Medicare benefits schedule, rTMS: repetitive transcranial magnetic stimulation

The referral rates were elicited from the expert advisory panel (AP). First the AP was asked to consider 'community psychiatrist referrals'. The question was: 'How will psychiatrists who would otherwise refer patients for ECT at private or public hospitals change their practice?' Will they choose to not refer some of these patients to hospital? Will they instead refer some patients to outpatients for rTMS or to a private clinic? Clearly if a patient needs to be hospitalised regardless of whether they have ECT, the availability of rTMS will not change the referring behaviour of the psychiatrist in this case. Of particular interest is the question of how many patients who would otherwise not be referred for ECT, but have SMTRD and remain in the community, will be referred for rTMS if it becomes available. Also of interest is will they be referred to the public or private sector. The assumptions elicited from the AP and used in the model (% referred) are presented in this table, as are the results when applied to the estimates of patients in each group.

Table 88 Community psychiatrists 'referrals'

	Current practice							
Rounding errors possible	Numbers in each group	Proportions (As % of all hospitalisations)	% not referred to hospital	Number to hospital	% referral to private clinic if rTMS available	% referred to public outpatients if rTMS available	Private clinic	Outpatients
oE(y) and oE(n) oH(y)				23,496				
SMDTR-hospitalised	25,375							
oH(y)	22,755	89.7%	0%	22,755				
Referred to public hospital	15,571	61.4%	0%	15,571				
Referred to private hospital	7,185	28.3%	0%	7,185				
oH(n)	2,619	10.3%		741				
Referred to public hospital	1,893	7.5%		517			344	1,032
Same-day	1,073	4.2%	90%	107	25%	75%	241	724
Multi-day	820	3.2%	50%	410	25%	75%	102	307
Referred to private hospital	727	2.9%		224			452	50
Same-day	348	1.4%	90%	35	90%	10%	282	31
Multi-day	378	1.5%	50%	189	90%	10%	170	19
oE(n) oH(n)	As % of all SMDTR							
Community patients	174,626	87.3%			4.5%	0.5%	7,858	873

ECT: electroconvulsive therapy, oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no), rTMS: repetitive transcranial magnetic stimulation, SMDTR: severely or moderately depressed treatment resistant

Table 89 presents the results of the AP's advice regarding referral choices by psychiatrists in hospitals. What percentage of patients who would otherwise have ECT but are required to remain in hospital will have rTMS? What about admitted patients who currently not having ECT? The estimates are assumed to be the same in the public and private sector in the base case.

Table 90 presents the results of the AP's advice regarding the proportion of patients who have rTMS and do not respond, who then go on to have ECT. It is assumed that these patients always have second line ECT at the site and type of admission they would otherwise have had ECT.

Table 89 Hospital psychiatrists 'referrals'

Rounding errors possible	Current numbers	Number referred if rTMS available	% have rTMS while admitted (or as outpatient or clinic if otherwise same-day)	Number have rTMS	Number have ECT	Number have neither
Derivation of estimates						
SMDTR-hospitalised	25,375	23,496		11,805.02	2,110	9,581
oH(y)	22,755	22,755		11,378	1,796	9,581
In public hospital	15,571	15,571		7,785	1,229	6,556
oE(y) oH(y)	2,459	2,459	50%	1,229	1,229	-
oE(n) oH(y)	13,112	13,112	50%	6,556	-	6,556
For patients in private hospital	7,185	7,185		3,592	567	3,025
oE(y) oH(y)	1,134	1,134	50%	567	567	-
oE(n) oH(y)	6,050	6,050	50%	3,025	-	3,025
oE(y)oH(n)	2,619	741		427	314	-
In public hospital	1,893	517		301	216	-
Same-day	1,073	107	90%	97	11	-
Multi-day	820	410	50%	205	205	-
In private hospital	727	224		126	98	-
Same-day	348	35	90%	31	3	-
Multi-day	378	189	50%	95	95	-

ECT: electroconvulsive therapy, oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no), rTMS: repetitive transcranial magnetic stimulation, SMDTR: severely or moderately depressed treatment resistant

Table 90 presents the results of the referral patterns specified by the AP as an expected uptake of rTMS and ECT following failure to respond to rTMS by site, type of admission and type of patient.

Table 90 Therapy for non-responders to rTMS

Rounding errors possible	Number of rTMS	Number of rTMS non-responders	% who have ECT after failing rTMS	Number who have ECT after rTMS failure	Responders	Total responders	% of all rTMS who have follow-up ECT
Admitted when rTMS available	2,224	1,156	50%	578	156	1,223	26.0%
Public hospital							
oE(y)	1,531	796	50%	398	107.15	842	26.0%
oE(y) same- day	97	50		25	6.76	53	26.0%
oE(y) multi-day	1,434	746		373	100.39	789	26.0%
Private hospital							
oE(y)	693	360	50%	180	48.52	381	26.0%
oE(Y) same-day	31	16		8	2.19	17	26.0%
oE(y) multi-day	662	344		172	46.32	364	26.0%
oE(y) but not admitted when rTMS available							
Outpatients or private clinics							
oE(y)	1,878	977	50%	488	131.47	1,033	26.0%
oE(y) same-day	1,279	665		333	89.55	704	26.0%
Public	966	502		251	67.61	531	26.0%
Private	314	163		82	21.95	172	26.0%
oE(y) multi-day	599	311		156	41.92	329	26.0%
Public	410	213		107	28.68	225	26.0%
Private	189	98		49	13.24	104	26.0%

ECT: electroconvulsive therapy, oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no), rTMS: repetitive transcranial magnetic stimulation, SMDTR: severely or moderately depressed treatment resistant

Table 91 represents the changed utilisation by site, sector and type of care that would otherwise have occurred. It separately reports patients who had ECT initially and those who had ECT following non-response to rTMS. The numbers are for patients. Patients who had two procedures are included once in the totals.

Table 91 Summary of referral patterns (figures represent patient numbers)

Care under policy 4 rounding errors possible	rTMS not available	rTMS available	Public hospital- if not rTMS				Private hospital if no rTMS				Not hospital
			Same-day ECT	Multi-day ECT	Multi-day no ECT	Total	Same-day ECT	Multi-day ECT	Multi-day no ECT	Total	No ECT
ECT											
No rTMS	6,212	2,110									
Public	4,351	1,445									
Same-day	1,073	11	11			11					
Multi-day	3,278	1,434		1,434		1,434					
Private	1,861	665									
Same-day	348	3					3			3	
Multi-day	1,513	662						662		662	
Post non response to rTMS		1,067									
Public		756									
Same-day		276	276			276					
Multi-day		479		479		479					
Private		311									
Same-day		90					90			90	
Multi-day		221						221		221	
rTMS (incl if follow-up ECT)		22,414									
Public		10,042									
Outpatient		2,257	821	512		1,333	31	19		50	873
Multi-day		7,785		1,229	6,556	7,785					
Private		12,373									
Clinic		8,686	241	102		344	314	170		484	7,858
Multi-day		3,687						662	3,025	3,687	
No rTMS or ECT	*193,788*	*175,475*									
Community	174,626	165,894									165,894
Multi-day											
Public	13,112	6,556			6,556	6,556					
Private	6,050	3,025							3,025	3,025	
Total patients	200,000	200,000	1,073	3,278	13,112	17,463	348	1,513	6,050	7,911	174,626

ECT: electroconvulsive therapy, oE(n): otherwise ECT (no), oE(y): otherwise ECT (yes), oH(y): otherwise hospital (yes), oH(n): otherwise hospital (no), rTMS: repetitive transcranial magnetic stimulation, SMDTR: severely or moderately depressed treatment resistant

Table 92 summarises the referrals by the number of patients who change their therapy following rTMS availability by the care they would otherwise have had. The most significant change is for patients who would have otherwise have same-day ECT. The reason that the rate of uptake is the same in the public and private hospitals is that the change in referrals is assumed to be the same.

Table 92 Change in therapy of total patients

	Public hospital if no rTMS				Private hospital if no rTMS				Not hospital	Total
	Same-day ECT	Multi-day ECT	Multi-day no ECT	Total	Same-day ECT	Multi-day ECT	Multi-day no ECT	Total	No ECT	
Number										
Do not change either therapy or site	11	1,434	6,556	8,001	3	662	3,025	3,690	165,894	177,586
Do not change therapy and/or site	1,062	1,844	6,556	9,462	345	851	3,025	4,221	8,731	22,414
Percent										
% who do not change either therapy or site	1%	44%	50%	46%	1%	44%	50%	47%	95%	89%
% who do change therapy and/or site	99%	56%	50%	54%	99%	56%	50%	53%	5%	11%

ECT: electroconvulsive therapy; rTMS: repetitive transcranial magnetic stimulation

Cost consequence and cost-effectiveness analysis of policy: results

This section identifies the costs, resource consequences and effect of the pattern of utilisation estimated in the previous section. This analysis culminates in an estimate of the ICER for no rTMS compared to rTMS available and subsidised at the applicant's proposed fee.

Table 93 looks at each sector of care when rTMS is not available, and identifies responders, and presents the total number of responders under rTMS by sector and admission type. It presents the analysis of resource use under the two policy options. The public hospital, PHI and MBS costs are also included. When compared to the duplication of the policy CEA in the published literature (Table 51), the differences between the two analyses are apparent. First, the number of procedures is significantly higher when oE(n) patients are included. Second, when we recognise that not all oE(y) patients who have rTMS will have it in the community, the bed days prevented are less. Finally, recognising that the effect of

ECT for patients who fail rTMS and who have a second-line ECT is less than the effect for a rTMS naïve patient, also reduces the additional responders. However, inclusion of the additional patient groups who would otherwise not have ECT, both of whom have an improved response rate, increases the number of responders per year.

Table 93 Number of responders to rTMS by sector and admission type

Care in absence of rTMS	Care when rTMS available	Scenario for change	Number in each group	As % of original group (rounding)	Responders at 3 months		Follow up ECT for rTMS non-responders
					No rTMS available	rTMS available	
Public, multi-day, ECT	Public, multi-day, ECT (38)	No change	1,434	44%	889	889	0
	Public, multi-day, rTMS (38)	1	1,229	38%	762	676	320
	Public, OPClinic, rTMS (38)	2	512	16%	318	282	133
	Private, clinic, rTMS (38)	3	102	3%	64	56	27
Public, same-day, ECT	Public, same-day, ECT (38)	No change	11	1%	7	7	0
	Public, OPClinic, rTMS (38)	4	821	77%	509	452	213
	Private, clinic, rTMS (38)	5	241	23%	150	133	63
Private, multi-day, ECT	Private, multi-day, ECT (38)	No change	662	44%	410	318	0
	Private, multi-day, rTMs (38)	6	662	44%	410	364	172
	Public, OPClinic, rTMS (38)	7	19	1%	12	10	6
	Private, clinic, rTMS (38)	8	170	11%	106	94	44
Private, same-day, ECT	Public, same-day, ECT (38)	No change	3	1%	1	1	0
	Public, OPClinic, rTMS (38)	9	31	9%	5	17	8
	Private, clinic, rTMS (38)	10	314	90%	47	172	82
Public, multi-day, no ECT	Public, multi-day, no ECT or rTMS (38)	No change	6,556	50%	983	983	0
	Public, multi-day, rTMS (38)	11	6,556	50%	983	3,147	0
Private, multi-day, no ECT	Private, multi-day, no ECT or rTMS (38)	No change	3,025	50%	454	454	0
	Private, multi-day, rTMS (38)	12	3,025	50%	454	1,452	0
Private, community, no ECT	Public community, no ECT or rTMS (38)	No change	165,894	95%	24,884	24,884	0
	Public, OPClinic, rTMS (38)	13	873	1%	131	419	0
	Private, clinic, rTMS (38)	14	7,858	5%	1,179	3,772	0

Table 94 Analysis of resource use under two policy options

Unit	All patients	Patients who would otherwise have ECT- by sector patient has rTMS			Patients who would NOT otherwise have ECT- by sector patient has rTMS							All patients ex community SMTRD- by sector patient has rTMS		
		Public	Private	Private	Otherwise hospitalised			Otherwise NOT hospitalised			Total	Public	Private	Total
					Public	Private	Total	Public	Private	Total				
Procedures														
ECT	-30,355	-19,333	-11,021	-30,355	0	0	0	0	0	0	0	-19,333	-11,021	-30,355
rTMS	268,974	31,351	17,873	49,224	78,672	36,302	114,974	10,478	94,298	104,775	219,750	110,023	54,175	164,198
Responders														
Loss	-287	-183	-104	-287	0	0	0	0	0	0	0	-183	-104	-287
Additional	6,043	0	0	0	2,163	998	3,162	288	2,593	2,881	6,043	2,163	998	3,162
Net	5,756	-183	-104	-287	2,163	998	3,162	288	2,593	2,881	6,043	1,981	894	2,875
Activity														
Multi-day seps.	-103	-135	32	-103	0	0	0	0	0	0	0	-135	32	-103
Bed days	-1,548	-2,031	483	-1,548	0	0	0	0	0	0	0	-2,031	483	-1,548
Same- day	-10,414	-6,307	-4,107	-10,414	0	0	0	0	0	0	0	-6,307	-4,107	-10,414
OPClinics	27,078	16,600	0	16,600	0	0	0	10,478	0	10,478	10,478	16,600	0	16,600
MBS consultations (39)	79,510	959	10,448	11,406	0	0	0	-2,619	70,723	68,104	68,104	959	10,448	11,406
Resources														
Health professional hours	74,618	-9,980	-5,689	-15,670	22,946	10,588	33,534	5,675	51,078	56,753	90,287	12,966	4,899	17,865
Tests	-6,071	-3,867	-2,204	-6,071	0	0	0	0	0	0	0	-3,867	-2,204	-6,071
Financing ($M)														
MBS ($M) (40)	12.87	-0.05	0.88	0.83	0.00	2.49	2.49	-0.15	9.71	9.56	12.05	-0.05	3.37	3.32
State ($M)	-1.34	-2.78	-1.71	-4.49	1.57	0.00	1.57	1.57	0.00	1.57	3.15	-1.21	-1.71	-2.91
PHI ($M)	-0.30	-0.20	-0.72	-0.92	0.00	0.63	0.63	0.00	0.00	0.00	0.63	-0.20	-0.09	-0.30
Total ($M)	11.24	-3.03	-1.55	-4.58	1.57	3.12	4.69	1.42	9.71	11.13	15.82	-1.46	1.57	0.11
ICER: $ per additional responder	1,952	n/a	n/a	n/a	n/a	n/a	1,483	n/a	n/a	3,863	2,618	n/a	n/a	37

Part IV Supply-side analysis

The objective of this analysis is to consider the supply of rTMS under a range of possible MBS subsidies.

The evaluation needed to provide estimates of utilisation and uptake and analysis that considered the capital costs of the equipment. Rather than assume that supply of the services would be equal to the demand (as predicted by referrals), the analysis considered the broad incentives to supply in any sector and the detailed incentives to supply rTMS at private clinics.

With regard to uptake in the public hospitals, if each of the 19 specialist psychiatric hospitals and 124 wards purchasing the equipment (AIHW 2005), this would represent a substantial national investment for rTMS in the order of $5M. The viability of supplying rTMS at specific public hospitals, if there is no consideration of volume of activity required, will depend upon local factors such as referrals to outpatients if it is provided in this way. Also, clinicians will vary in their decisions to use rTMS depending upon the trade-off in additional bed days vs foregone responders. Finally, it will depend on the financing arrangements in specific hospitals. No formal analysis was performed.

With regard to private hospitals, the viability of supplying the service will depend upon the difference in revenue and costs for the two procedures (ECT and rTMS) if performed in hospital and the difference in revenue and cost for the admissions that ECT admissions are replaced with. It may also depend upon the arrangements with anaesthetist in private psychiatrists who may change the unit cost of their services if less services are required. It is highly likely to be financially viable to use rTMS for patients who are depressed, have multi-day admissions and are currently not using ECT. For these patients, provided the rebate is greater than the costs of provision, which is likely under Policy 4, it will increase the net income to the hospital associated with the admission. It is possible that the private hospitals could establish on site clinics, not same-day as no GA is required, and continue to receive revenue from these patients.

The financial viability of rTMS private clinics, whether specialist high volume or standard constancy based psychiatric clinics, is the key issue from the supply side. For a given demand for the service from patients who would otherwise have ECT or are hospitalised and cannot have ECT:

- the larger the number of clinics that have rTMS machines and the more profitable it is to provide the service;

- the more patients who would otherwise be in the community and not have ECT will have rTMS.

The base case of the model specifies that 5 per cent of oE(n)oH(n) patients will have rTMS and given there are more than 170,000 in this group, even a small increase in referrals could have a significant impact on the number of rTMS procedures nationally. From a cost-effectiveness perspective, this change will increase the response rate and increase the cost to the MBS and the effect on the ICER will be to increase it. From a total expenditure perspective, it will increase the cost to the MBS for rTMS significantly.

Table 95 presents the number of beds and sites for mental health patients in Australia.

Table 95 Number of beds and sites for mental health patients in Australia

	Number of units	Number of available beds	Average beds per site
Public psych hospitals	19	2,561	135
Public acute hospitals (with specialised psych unit)	124	3,463	28
Total public		6,024	
Private psych hospitals	25	1,441	58
Govt residential care services	246	1,246	5

Table 96 Numbers of psychiatrists, patients and consultations in Australia

Psychiatrists	
Psychiatrists (private)	1062
Psychiatrists (public)	1758
Total	2820
MBS consultations with psychiatrists	1,700,000
MBS consultations per FTE private	1,601
Per year	
MBS consultations per week	33
Patients per FTE psychiatrist	
Number of SMDTR patients	200,000
Ratio of SMDTR patients per FTE psychiatrist	71
Number of oE(y) patients	6,212
Ratio of oE(y) patients per FTE psychiatrist	2.2
Number of oE(n) oH(y) patients	19,162
Ratio of oE(n) oH (y) patients per FTE psychiatrist	6.8

FTE: full-time equivalent; SMDTR: severely or moderately depressed treatment resistant

Table 96 uses estimates of the number of psychiatrists in Australia to determine a few indicators. In particular, there are around 71 SMTRD patients per FTE psychiatrist and around 2.2 patients who would otherwise have ECT per FTE psychiatrist and around 6.8 patients who are hospitalised for depression but do not have ECT. There is then a very small base of patients on a per FTE psychiatrist basis who are in the oE(y) group. The source of the estimate for number of psychiatrists is AIHW (2005).

The utilisation of private clinic services, estimated from the expected referral rates provided by the AP and analysed in the previous section, are presented in Table 97.

Table 97 Utilisation of private clinic services

Total	Numbers
Patients	8,686
Sessions	104,229

The cost of equipment to a clinic was by estimated by: determining the loan that would be required; the annual maintenance costs; and the annual loan repayments if the loan were repaid by the practice in 4 years. At this time, 4 years, the coils would need to be replaced, but this is not considered in the analysis.

Table 98 Costs of rTMS equipment

Present value of machine	$40,000
Cost of replacement coils	$4,000
Replacement years for coils	4
Maintenance	$500
Years to replacement	10
Relevant interest rate	10%
Loan for private provider (years)	4
Annuity for private provider (excl. maintenance)	12,619
Annuity for private provider (incl maintenance)	$13,119
Repayment at end of year one	$44,000

The four policy options set out in Table 87 were used to estimate the additional MBS revenue to a practice compared to the MBS revenue they would have received had they provided a 15- to 30-minute consultation instead. The net MBS rebate was used in the remaining analyses.

Table 99 Rebate for procedure for the four policy options

Policy	MBS rebate for procedure	MBS rebate foregone (from consultation)	Net MBS rebate
Policy 1	$0	$65	-$65
Policy 2	$65	$65	$0
Policy 3	$53	$65	-$12
Policy 4	$128	$65	$63

The number of patients that could be treated each year was estimated by first making assumptions about: the number of weeks per course, weeks per year, an adjustment for capacity, the number of cycles (a cohort of patients starting a 2.5 week course of treatment) and the maximum number of patients that could be in a cohort (Table 100).

Table 100 One year utility of one rTMS machine

Activity in one year (per machine)	
Weeks for one course	2.5
Weeks available per year	48
Capacity adjustment	80%
Maximum patients per cycle (cycle is a period where one cohort of patients go from start to finish for course)- per day max	16.00
Cycles per year (capacity adjusted)- of length	15
Patients per year	197
Psychiatrist time per treatment (hours)	15 to 30 min consult

The additional costs of operation (the repayments, plus maintenance plus cost of operator) were compared to the MBS revenue under each policy option. The net income from providing the service at capacity was estimated. In the base case we assumed that there would be no additional costs of the operator compared to a consultancy only clinic,

because there would have been a nurse available in that practice otherwise. The tasks of the nurse would change, but the total time required would not.

The additional above rebate fee that would be required was estimated, per session and per course, in order to make a practice operating at capacity breakeven. This patient fee above rebate is more than that which would occur in a standard psychiatric consultation. In policy 4 this is a negative result which indicates that this proposed MBS fee is more than breakeven at this capacity (Table 102).

Table 101 Additional MBS rebate revenue for each policy at maximum capacity

Maximum capacity (one FTE psychiatrist)	
Maximum cycles per year	15
Maximum patients per cycle (capacity adjusted) (41)	16
Maximum patients per year (capacity adjusted)	197
Treatments	2,359
Additional MBS rebate revenue (above consultations only clinic)	
Policy 1 (42)	-$153,213
Policy 2 (43)	$0
Policy 3 (44)	-$28,477
Policy 4 (45)	$147,598
Additional cost (46)	$13,119
Operator (annual)- costs above non procedural clinic (47)	$0
Machine (annuity payment) (48)	$13,119
Additional MBS revenue less additional service costs	
Policy 1 (42)	-$166,332
Policy 2 (43)	-$13,119
Policy 3 (44)	-$41,596
Policy 4 (45)	$134,479

Table 102 Breakeven above rebate patient fee

Policy	Breakeven ARPF (Per course) (49)
Policy 1 (42)	
Per session	$71
Per course	$846
Policy 2 (43)	
Per session	$6
Per course	$67
Policy 3 (44)	
Per session	$18
Per course	$212
Policy 4 (45)	
Per session	-$57
Per course	-$684

The objectives of the analysis presented in Table 103 were to identify the revenue to the clinic and the breakeven number of patients per clinic for a nominated above rebate fee (also above the fee that would be paid by the patient for a standard consultation), in the base case $20 and $30, but this can be varied. In addition, the number of sites that could be supported at breakeven capacity was estimated, given the total expected demand based on the analysis in Part III. Policy 1 would not be feasible, but the remaining policies would, with policy 4 resulting in a surplus (revenue less costs including opportunity costs of foregone consultations) of around $200,000 per year while repayments are being made. At an additional fee of $30, the number of patients per clinic required to breakeven was 36, 61 and 12 for polices 2, 3 and 4 respectively. The number of single machine clinics or machines that could be supported would be 238, 142 and 735 for polices 2, 3, and 4 respectively. The total market for rTMS machines in the private sector, outside the hospitals, could be up to $29.5M under policy 4. There would be a market incentive to increase the number of clinics that have machines under policies where a smaller number of patients are required to breakeven.

Table 103 Breakeven patients required for machines required for each policy

Solve for surplus and breakeven patients at nominal Above Rebate Patient Fees (ARPF)		
Nominated ARPF per session (50)	$20	$30
ARPF per course of 12 treatments (51)	$240	$360
Patients- max capacity adjusted (53)	197	197
ARPF revenues (54)	$47,186	$70,779
Surplus or deficit above consultancy only clinic for a given ARPF (52)		
Policy 1 (42)	-$119,146	-$95,553
Policy 2 (43)	$34,067	$57,660
Policy 3 (44)	$5,590	$29,183
Policy 4 (45)	$181,665	$205,258
Breakeven patients, number of sites and market for machines at nominal copay (55)		
Policy 1 (42)		
Breakeven patient (55)	n/a	n/a
Sites that could support expected patients at breakeven (56)	n/a	n/a
Market for machines (57)	n/a	n/a
Policy 2 (43)		
Breakeven patient (55)	55	36
Sites that could support expected patients at breakeven (56)	159	238
Market for machines (57)	$6,356,000	$9,534,000
Policy 3 (44)		
Breakeven patient (55)	138	61
Sites that could support expected patients at breakeven (56)	63	142
Market for machines (57)	$2,520,154	$5,698,154
Policy 4 (45)		
Breakeven patient (55)	13	12
Sites that could support expected patients at breakeven (56)	656	735
Market for machines (57)	$26,237,568	$29,415,568

Finally, at the nominated patient fees of $30 and the total expected number of patients of 8,780, a total of 45 machines operating at capacity could be supported. The national surplus (as defined elsewhere) under this scenario would be $2.6M, $1.3M and $9.1M respectively (Table 104)

This analysis of supply side issues should be considered illustrative rather than predictive.

Table 104 The number of sites that can be supported with expected private clinic patients

Nominated ARPF per session (58)	$20	$30
ARPF per course (59)	$240	$360
Sites supporting expected private clinic patients, at maximum capacity (60)		
Expected patients (41)	8,686	8,686
Maximum patients per site (capacity adjusted) (41)	197	197
Sites supporting expected patients-sites operating at maximum capacity (61)	44	44
Size of market for machines in private sector at max capacity (62)	$1,767,122	$1,767,122
National surplus above consulting only clinic at max capacity (adj) and nominated ARPF and max sites (63)		
Policy 1 (42)	-$5,263,621	-$4,221,330
Policy 2 (43)	$1,505,018	$2,547,309
Policy 3 (44)	$246,972	$1,289,264
Policy 4 (45)	$8,025,592	$9,067,883

Appendix J Reference input table

Ref. in table	Derivation and/or sources
1	The additional responders are patients who would otherwise not responded had only ECT been available. This is estimated using the report's estimate of the expected treatment effect for rTMS vs ECT and the probability of response to ECT from cohort studies. It is assumed, as is the case in the published study but not the application's full analysis, that all patients who are non-responders to first line rTMS go on to have ECT and their response rate is the same as if they had ECT as baseline (derived from Table 63).
2	The additional cost of rTMS to the MBS assumes that all activity occurs in private hospitals under both strategies (derived from Table 63).
3	Reference (2) divided by reference (1).
4	The savings due to the reduction in hospital days. This assumes that 20 days in hospital are prevented as all rTMS patients have care in the community as described in Kozel et al 2004 (derived Table 63).
5	The number of bed days for ECT was assumed to be the same in public and private sector. The inputs and resource use for different types of care can be seen in Table 67 and Table 68.
6	The number of outpatient clinic sessions is assumed to be 10 per patient in a cycle of care.
7	The number of consultations includes consultations at would have occurred in private hospitals for patients who would otherwise not have ECT, and community consultations post discharge and for patients who would otherwise be cared for in the community.
8	Provider hours includes consultations with psychiatrists. The hours per type of care are in Table 67 and Table 68. There is a reduction in person hours per session for rTMS compared to ECT.
9	Tests are detailed in Table 67 and Table 68 and only additional tests that would otherwise not occur, including X rays, are included.
10	The MBS costs are detailed in Table 83.
11	The financial costs to public hospital funders are detailed in Table 81.
12	The private health insurer financial costs are detailed in Table 84.
13	The number of patients in Australia who have moderate to severe depression and are refractory to one or two courses of antidepressants (see Table 75).
14	No rTMS: The number of patients who have at least one admission that is multi day, for depression, regardless of whether they have ECT, was derived separately for public and private sectors then summed and then divided by number who have SMTRD depression. The number of patients in public sector was derived by: 1) the AN-DRG data on admissions for multiday ECT, each patient has one course. 2) Use expert opinion to determine the percentage of all patients who are SMTRD and admitted who have ECT 3) Back solve from the estimate of the number of people who have ECT to work out the total number of patients. 4) Double checked by taking the estimate of the number of separations within the principle diagnosis of depression and then working out the implied average number of admissions per patient per year. Expert opinion agreed with this was a reasonable estimate. Private estimates similarly performed; except an adjustment was made for the evidence from MBS data that one course of ECT occurs over two or three admissions in private sector. See also Table 78 (Patients by group divided by the total number of SMDTR patients).
15	No rTMS: The percentage of patients who have private treatment was estimated by dividing (the number admitted multiday in each sector) by (total number admitted multiday for depression) (see Table 79).
16	No rTMS: Those who do not have a multiday admission for depression were then allocate to either no admission for ECT or admission for ECT - reference to same day admissions data from AIHW (public) and MBS (private) (see Table 79).
17	No rTMS: The percentage of multiday day public admitted was estimated by dividing (the number of patients who had ECT in public sector as multiday) by (the total number admitted at least once with a principle diagnosis of depression), derived as described above.
18	No rTMS: The percentage of multiday day who were privately admitted was estimated by dividing (the number of patients who had ECT in public sector as multiday) by (the total number admitted at least once with a principle diagnosis of depression), derived as described above.
19	No rTMS: The number of multiday admissions for ECT estimated using procedure data was allocated using expert option to either (require admission regardless of need for ECT) or (require admission only for ECT). Only the latter are in this group. The sameday were estimated from AN-DRG data and added together to find the total number in these two groups.

20	No rTMS: The number of multiday admissions for ECT estimated using procedure data was allocated using expert option to either require admission regardless of need for ECT or require admission only for ECT. Only the latter are in this group. The same day were estimated from MBS data and added together to find the total number in these two groups.
21	The three month response rate for ECT was derived from expert opinion and published literature (see Table 20).
22	The three months response rate for pharmacotherapy or no pharmaco therapy for SMTRD was from study referred by expert opinion (see Table 47).
23	The percentage of all patients who are admitted for depression, multiday, regardless of requirement for ECT remains the same with and without rTMS. This split is not affected by the change in referral patterns, only by the characteristics of the SMTRD patients.
24	rTMS: The percentage of the above group who are admitted as either private or public remains the same with as without rTMS. For those who DO NOT have a multiday admission to treat their depression, this is the split between the public sector ECT (same day or multiday- only those who need multiday admission due to ECT requirements), private sector ECT (same day or multiday - only those who need multiday admission due to ECT requirements) and no hospital events but community treatment. (derived from output of simulations on effect of changed referral patterns, as presented in Table 91 Summary of referral patterns without rTMS compared to rTMS (unconstrained referrals).
25	rTMS: 50 per cent of the above group were assumed to have rTMS, some of these patients would otherwise have had ECT and others would otherwise had no ECT while admitted. The change d referrals by hospital psychiatrists when rTMS is available are derived from expert opinion, applied to existing numbers of patients in each group, and the product is presented in this decision tree (see also Table 89).
26	rTMS: The changes in referral behaviour within the hospitals are in the base case assumed to be the same for private and public hospitals.
27	rTMS: There are three changes in referrals relevant here - referrals by community psychiatrists to community rTMS instead of same day ECT or multiday ECT, treatment by hospital psychiatrists who will opt for rTMS for some patients who would otherwise have ECT (see also Table 91).
28	rTMS: The changes in private and public are assumed to be identical in the base case.
29	rTMS: 100 per cent of these patients then have their care as multiday admissions.
30	rTMS: The proportion who have multiday admission in this group is higher than would otherwise be the case as those who can have rTMS as outpatient, particularly most of the patients who would otherwise have been same day ECT (see also Table 91).
31	rTMS: All rTMS in public hospitals was assumed to occur in outpatient clinics.
32	rTMS: Similarly as for 31 above, except patients who have rTMS have it in private community sector.
33	All rTMS in private sector is not as outpatient in private hospital but in a clinic where the MBS rebate is higher.
34	The percentage who are non-responders to rTMS is determined from the clinical trial estimate of treatment effect applies to the response rate for ECT (see Figure 17 and Table 20).
35	If patients are non-responders to rTMS, some are assumed to have follow up ECT, and they have ECT in the same site they would otherwise have had. This site is not specified in this tree as there would be too many branches.
36	Response rate to rTMS is the response rate to ECT treatment effect (see Table 20).
37	If people have rTMS and do not respond they are assumed to be non responders at 3 months and if they are non-responders to rTMS and have ECT their response rate to post rTMS ECT is constrained by the overall response rate to ECT (see Table 20).
38	The number of people in each group are sourced in Table 20 and the result of their care is presented separately for rTMS and follow up ECT if relevant, using the treatment effect table.
39	Additional MBS consultations are the combined effect of additional consultations due to 12 rTMS rather than 10 ECT treatments per cycle, ECT for non-responders, consultations that would otherwise have occurred for patients who stay in community etc.
40	The additional costs to the MBS take into account both the additional consultations and the consultations that would otherwise have occurred (see also Table 83).
41	Expected number of community patients is estimated as the result of changes in referral patterns by community and hospital psychiatrists and the current number of patients per site and sector.
42	Policy One is no MBS subsidy for either the rTMS procedure or for the consultation in which it occurs. Revenue from patient payments only. The opportunity cost of the consultations is any additional patient fee (assumed to be 0) less the MBS rebate that would otherwise have been received for that consultation. See also Table 87.

43	Policy Two is a MBS subsidy that is equivalent to the payment for a Psychiatrist for an ECT. The surplus is the additional patient fee (assumed to be 0) plus the MBS rebate for rTMS less the rebate that would have been received had the psychiatrist instead provided an ordinary consultation. See also Table 87.
44	Policy Three is payment for the consultation -There is no surplus as the psychiatrist receives what they would otherwise have received in a consultation only clinic, unless there is an additional patient fee above what would otherwise have been paid. See also Table 87.
45	Policy Four is payment for the consultation and procedure as one rebate at the requested amount. The surplus is the additional patient fee over and above what would otherwise have been received (assumed to be 0) plus the MBS rebate les the rebate that would have been received had a consultation only been provided. See also Table 87.
46	The additional cost of the operator and the loan repayments (derived within the table).
47	In the base case we assumed that the additional costs to a clinic are no greater than the costs that would be incurred had it been a consulting only clinic as the operator could be a trained practice nurse.
48	This is the annual payment on a loan for this equipment, assuming the loan is paid off in 4 years and the rate of interest is 10%. This does not take into account any tax consequence of depreciation (see also Table 98).
49	The fee to be paid by patients, above the rebate, such that the clinic breaks even at maximum capacity for each policy. Derived from (revenue required to break even at policy at additional costs of rTMS) divided by (maximum number of patients).
50	The willingness of patients to pay a fee above the rebate is a determinant of supply. Two possible values are tested ($20 and $30).
51	The amount of above rebate fees over 12 treatments, derived from (reference (50) above) multiplied by (the number of sessions in a cycle of rTMS).
52	The total surplus from previous table plus the patient revenue.
53	The total number of patients annually at a clinic operating at capacity (patients at maximum capacity, adjusted by assuming operating slightly below capacity). See also Table 101.
54	The total revenue from patients at the fee of either $20 or $30 and at maximum patients.
55	Breakeven patients are the number of patients who could have rTMS if a site operated at breakeven for the given policy – just to support the additional costs of rTMS. There is still a profit to the provider but this is the same as that if the clinic were providing standard consultations only. For each policy, N/A means no breakeven.
56	The number of sites is the number of expected patients nationally divided by the number of breakeven patients per site (corresponding to the number of sites that could be operating in Australia with breakeven patients).
57	The number of machines that would be sold if all sites were operating at breakeven. The market for machines is (the cost per machine) multiplied by (the expected number of breakeven machines).
58	The willingness of patients to pay a fee above the rebate is a determinant of supply. Two possible values are tested ($20 and $30).
59	The amount of above rebate fee over 12 treatments. This is derived by (the above fee) multiplied by (the number of sessions in a cycle of rTMS).
60	The number of sites, each operating at maximum capacity, which could support all expected patients. Assuming that sites are all operating at maximum, this is (the expected number of community rTMS patients) divided by (the maximum patients per site) is the maximum number of sites. This is discussed in more detail in Appendix I.
61	The number of sites, each operating at maximum capacity, which could support all expected patients. (Expected patients) divided by (capacity for patients).
62	The number of machines by cost per unit to give the total size of the market. (Expected number of machines) multiplied by (the average market price of machines).
63	The national surplus is the surplus per consultation above that which would have occurred in a consultation only clinic, assuming that the patient fee is above what would otherwise be paid by a patient, multiplied by the total number of sessions in Australia.

Abbreviations

AD	anti-depressant
ANOVA	analysis of variance between groups
APA	American Psychiatric Association
AIHW	Australian Institute of Health and Welfare
AR-DRG	Australian Refined Diagnostic Related Group
ARPF	above rebate patient fee
ARTG	Australian Register of Therapeutic Goods
BDI	Beck depression inventory
BPRS	brief psychiatric rating scale
CBT	cognitive behavioural counselling
CEA	cost-effectiveness analysis
CI	confidence interval
cr	case report
cs	case series
CXR	chest x-ray
DALY	disability-adjusted life year
DLPFC	dorsolateral prefrontal cortex
DSM-VI	Diagnostic and Statistical Manual of Mental Disorders (version 4)
ECT	electroconvulsive therapy
EEG	electroencephalogram
FDA	Federal Drug Administration
GA	general anaesthetic
GAF	global assessment of function
GDR	global depression rating
HDRS	Hamilton depression rating scale
HIC	Health Insurance Commission
HT	health technology
HTA	health technology assessment
Hz	Hertz
ICD-10	International statistical Classification of Diseases and related health problems (version 10)
ICER	incremental cost effectiveness
IQ	intelligence quotient
IPSRT	interpersonal and social rhythm therapy
MAOI	monoamine oxidase inhibitors
MBS	Medicare benefits schedule
m'day	multi-day
MEP	motor-evoked potential
MSAC	Medical Services Advisory Committee
MT	motor threshold
NA	not applicable
NARI	noradrenaline reuptake inhibitors
NaSSA	noradrenaline serotonin specific anti-depressants
ND	not determined
NHMRC	National Health and Medical Research Council
NR	not reported
NS	not significant
OP	outpatient

PHI	private health insurers
PSQI	Pittsburgh sleep quality index
QALY	quality-adjusted life year
QIDS-SR-16	Quick Inventory of Depressive Symptomatology – Self Report
RCT	randomised controlled trial
RIMA	reversible inhibitors of monoamine oxidase – A
RR	relative risk
rTMS	repetitive transcranial magnetic stimulation
SD	standard deviation
s'day	same day
SMDTR	severely or moderately depressed treatment resistant
SNRI	serotonin and noradrenaline reuptake inhibitors
SSRI	selective serotonin reuptake inhibitors
TCA	tricyclic anti-depressants
TGA	Therapeutic Goods Administration
TMS	transcranial magnetic stimulation
VAS	visual analogue scale
WAIS	Wechsler adult intelligence scale
WHO	World Health Organisation
WMD	weighted mean difference
YLD	years lived with disability
YMRS	Young mania rating scale
UK	United Kingdom

Units of measurement

[ ]	standard deviation
( )	range
{ }	unit of variance not stated
mm	millimetres

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