Repetitive Transcranial Magnetic Stimulation for Treatment Resistant Depression

A Health Technology Assessment

The Health Technology Assessment Unit, University of Calgary

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Abbreviations

BDI	Beck Depression Inventory
CANMAT	Canadian Network for Mood and Anxiety Treatments
CGI	Clinical Global Impression
CI	Confidence Interval
DLPFC	Dorsolateral Prefrontal Cortex
DSM	Diagnostic and Statistical Manual
EAP	Employee Assistance Program
ECT	Electroconvulsive Therapy
HAMD	Hamilton Depression Rating Scale
HPSP	Health Services and Health Professional Strategy and Practice
ICER	Incremental Cost Effectiveness Ratio
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major Depressive Disorder
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
RCT	Randomized Controlled Trial
rTMS	Repetitive Transcranial Magnetic Stimulation
SPECT	Single Photon Emission Computed Tomography
TRD	Treatment Resistant Depression

Executive Summary

Purpose: This report summarizes the findings and conclusions of a provincial review on the use of repetitive transcranial magnetic stimulation (rTMS) for treatment resistant depression (TRD), conducted to inform the Alberta Health Technologies Decision Process. The primary policy question for this report was: *Should repetitive transcranial magnetic stimulation be established as a publicly funded service for people with treatment resistant depression?*

Background:

- Recent statistics from Statistics Canada, based on the 2012 Canadian Community Health Survey, indicate that 4.7% of the Canadian population aged 15 and over met the criteria for a major depressive episode in the past 12 months.
- Based on the epidemiological data available, between 30-60% of people with a Major Depressive Disorder (MDD, described as two or more episodes of depressed mood that lasts for a period of two weeks or longer) will have TRD (depression which does not to subside with adequate pharmaceutical and behavioural treatment).

Technology under Consideration

- rTMS is a non-invasive procedure in which cerebral electrical activity is influenced by a rapidly changing magnetic field.
- The magnetic field is created by a plastic-encased coil which is placed over the patient's scalp. rTMS therapy was approved by Health Canada for clinical delivery in Canada in 2002. Currently, two rTMS machines are licensed without any age or clinical indication restrictions.

Methods:

- Key informant interviews were conducted with twelve individuals to collect information on the current social context in Alberta, including the burden of illness and current patterns of care. The participants included individuals working in Edmonton, Calgary, Ponoka and Grande Prairie.
- A systematic review of the literature was conducted to determine the efficacy of rTMS in comparison to other available alternatives for adults with TRD. A meta-analysis was conducted using a random-effects model to estimate the overall pooled effect size.

- A systematic review of the literature was conducted to determine the efficacy of rTMS in comparison to other available alternatives for youth and young adults with TRD.
- To determine the cost-effectiveness, simple economic models were used to compare Electroconvulsive Therapy (ECT), rTMS, and standard therapy (antidepressant treatment). The likelihood of response and remission with each treatment was included. The primary outcome was the cost per quality-adjusted life year (QALY) gained. Probabilistic sensitivity analysis was conducted to determine the overall uncertainty in the model.

Results:

- Key informants feel that rTMS should be considered as one treatment option as part of the overall care pathway for patients with MDD and TRD. rTMS is currently being provided to adults with TRD at two locations in Alberta, the Centennial Centre in Ponoka (funded publicly) and the Riverview Medical Clinic in Calgary (funded privately). rTMS is available to youth and young adults in the context of research through the Alberta Children's Hospital.
- Adults with TRD: 786 abstracts were identified, 184 were reviewed in full-text, and 70 randomized controlled trials were included. The included studies were of moderate quality, with most having a combination of unclear and low risks of bias, and few having high risks of bias.
    - rTMS is twice as likely to result in response (RR: 2.35 [95% Confidence Interval {CI}: 1.70-3.25]) and remission (RR: 2.24 [95% CI: 1.53-3.27]) than a sham procedure. However, the optimal rTMS treatment protocol remains unclear with no statistically significant differences in the pooled estimates of response and remission rates between high and low frequency rTMS (response RR: 1.19 [95% CI 0.97-1.46], remission RR: 1.29 [95% CI 0.75-2.22]), unilateral and bilateral rTMS (response RR: 1.15 [95% CI 0.85-1.56], remission RR: 1.18 [95% CI 0.71-1.96]), and high and low intensity rTMS (response RR: 1.15 [95% CI 0.54-2.41], remission RR: 1.72 [95% CI 0.89-3.33]).
    - None of the included studies reported serious side effects; minor side effects reported were mild headaches and discomfort during the procedure.
    - Few studies have reported on the effectiveness of rTMS compared to ECT (n=3). The pooled estimates for response and remission provide conflicting results indicating rTMS may be more effective at achieving response but less effective at achieving remission. The effectiveness of rTMS compared to ECT remains unclear.

    - rTMS is more costly and more effective than sham at achieving response and remission with a cost per QALY gained of $13,084 and $20,203, respectively. When comparing rTMS to ECT, rTMS is less costly and more effective than ECT at achieving response (ECT has a cost per QALY gained of $328,325 compared to rTMS). There is some uncertainty in the model due to uncertainty in the relative risks estimates of rTMS for both response and remission.
- Youth and young adults with TRD: 140 abstracts were identified, 26 were reviewed in full-text and 3 cohort studies were included. These studies were conducted in Israel, the United States and Australia between 2008 and 2012. The studies suggest that rTMS may be effective; however, further high quality studies are required.

Conclusions: Inequitable access to rTMS exists within Alberta. In adults with TRD, rTMS is more effective than no treatment but the optimal protocol remains unclear. No statistically significant differences were found between rTMS and ECT; it is unclear which is most efficacious. The cost per QALY gained with rTMS compared to sham is $13,084 for response and $20,203 for remission. rTMS is more effective and less costly than ECT the majority of the time. The total fixed investment for 1 rTMS machine, including fixed operational costs, is $175,500. The marginal cost for the first session is $132.33 and the marginal cost for ongoing sessions is $47.60 (accounting for 15 minutes of nursing time). An estimate of demand is unknown. The effectiveness in youth and young adult populations is uncertain.

1 Purpose of this Health Technology Assessment

The purpose of this health technology assessment (HTA) is to summarize the available evidence on repetitive transcranial magnetic stimulation (rTMS) for individuals with treatment resistant depression (TRD). The report includes evidence on the social impact of rTMS, the efficacy, safety, and cost-effectiveness of rTMS in comparison to available alternatives for both adult and youth/young adult patients with TRD.

1.1 Policy Question and Research Objectives

Primary ***policy question*** to be answered by this HTA is:

- Should repetitive transcranial magnetic stimulation (rTMS) be established as a publicly funded service for people with treatment resistant depression?

Primary ***research questions*** to be answered by this HTA are:

- What is the burden of illness of TRD in Alberta?
- What are the patterns of care and capacity to deliver service in Alberta as they relate to TRD?
- What is the safety and effectiveness/efficacy of rTMS compared with drug therapies and electroconvulsive therapy (ECT) for people with TRD?
- What is the cost-effectiveness of rTMS compared with drug therapies and ECT for people with TRD?
- What is the budget impact of provision of rTMS for people with TRD?

2 Background Information

2.1 Major Depressive Disorder

Depression is a common mental disorder[1]. The Canadian Mental Health Association defines depression as "a mood disorder represented by feelings of sadness, loneliness, despair, low self-esteem, withdrawal from interpersonal contact with others, and symptoms such as difficulty sleeping and decreased appetite"[2]. Symptoms of depression include loss of focus, lack of energy, complaints of physical illness with no cause, and thoughts of suicide[3]. Globally, more than 350 million people of all ages suffer from depression[4]. Depression is the leading cause of disability worldwide, and is a major contributor to the global burden of disease[4]. In Canada, the burden of disease for depression is almost twice that of heart disease[5], with the lifetime prevalence of major depression estimated to be between 10.8[6] and 12.2%[5]. The condition is more common among women than men[7]. Recent statistics from Statistics Canada, based on the 2012 Canadian Community Health Survey, indicate that 4.7% of the Canadian population aged 15 and over met the criteria for a major depressive episode in the past 12 months[8]. Individuals may experience single or multiple episodes of depression throughout their lifetime[2].

According to the Diagnostic and Statistical Manual of Mental Disorders 4th edition, Text Revision (DSM-IV-TR) criteria, Major Depressive Disorder (MDD) is described as two or more episodes of depressed mood that last for a period of two weeks or longer, and is accompanied by clinically significant impairment in everyday function, work and social interactions[9]. Major depression has a high relapse rate, with recurrent episodes associated with an increased risk or chronicity and often resulting in long-term psychosocial impairment and distress, loss of productivity, and suicide[10].

2.2 Risk Factors for Major Depressive Disorder

There are a number of risk factors for MDD including[5;11]:

- Depression that starts in childhood or adolescence;
- Low socioeconomic status;
- A history of anxiety disorder, borderline personality disorder or post-traumatic stress disorder;
- Abuse of alcohol or illegal drugs;
- Personality traits such as having low self-esteem, being overly dependent, self-critical or pessimistic;
- Serious or chronic illness, such as cancer, diabetes or heart disease;
- Certain medications, such as some high blood pressure medications or sleeping pills;

- Traumatic or stressful events, such as physical or sexual abuse, the loss of a loved one, a difficult relationship or financial problems; and,
- A family history of depression, bipolar disorder, alcoholism or suicide.

2.3 Diagnosis of Major Depressive Disorder

Many people with MDD, and depression more generally, go undiagnosed or undertreated[5;12]. Contributing factors to this include a lack of help-seeking due to social stigma and/or lack of knowledge, a lack of access to evidence-based interventions, and a shortage of trained professionals[5].

A number of validated, clinician administered and self-rating tools are available to assist in the diagnosis of depression, and to assist in measuring severity. Clinician administered tools widely used include the Hamilton Rating Scale for Depression (HAMD)[13] and the Montgomery-Asberg Depression Rating Scale (MADRS)[14]. Self-rating tools include the Quick Inventory of Depressive Symptomatology[15], the Beck Depression Inventory (BDI)[16], the Geriatric Depression Scale[17], and the Patient Health Questionnaire (PHQ-2 and PHQ-9)[5].

These tools all have limitations and can only be considered as aids in diagnosis. Screening results must be considered in context, considering an individual's life circumstances, symptoms and any specific medical conditions[18].

2.4 Current Care Patterns for Major Depressive Disorders

Since depression symptoms vary amongst patients, no one treatment option works for all patients with MDD[19]. Treatment is often defined as "acute" or "maintenance", depending on the purpose of the treatment; the goal of acute treatment is for the patient to experience remission (no symptoms of depression) while the goal of maintenance treatment is to address any symptoms that arise and to keep the patient in remission[6].

Possible treatment options for MDD include pharmaceuticals (e.g. tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and reversible inhibitors of monoamine oxidase), cognitive behaviour therapy, interpersonal psychotherapy , and electroconvulsive therapy (ECT)[19]. The Canadian Network for Mood and Anxiety Treatments (CANMAT) recommends that selective serotonin reuptake inhibitors, and serotonin and noradrenaline reuptake inhibitors should be used as first-line antidepressant treatments[20]. Talk therapies, such as cognitive behaviour therapy and interpersonal therapy, may be used alone or in combination with pharmaceuticals. There is a strong body of evidence supporting the effectiveness of talk therapies in the treatment of depression[21].

ECT is generally used, in selected patients, when patients do not adequately respond to pharmacotherapy and talk therapy[22]. In ECT, controlled electric current is allowed to pass through the patient's brain with the goal of alleviating symptoms of severe depression or suicidal tendencies.

2.5 Treatment Resistant Depression

Based on the epidemiological data available, between 30-60% of people with a MDD will have TRD[23;24]. TRD is broadly used for patients who have been diagnosed with a MDD, but who fail to experience sufficient relief after adequate rounds of medication[23]. The definition of TRD has not been standardized and in practice the definition varies from lack of response to 1 antidepressant trial to requiring patients to fail at least 3 adequate antidepressant trials[24].

Severity of treatment resistance can be staged using a method developed by Thase and Rush[25]. This method uses stages 1-5 to describe severity of treatment resistance[25]. Thase and Rush define the stages of TRD as follows[25]:

Stage 1: "Failure of an adequate trial of 1 class of major antidepressant"

Stage 2: "Failure of adequate trials of 2 distinctly different classes of antidepressants"

Stage 3: "Stage 2 plus failure of a third class of antidepressant, including a tricyclic antidepressant"

Stage 4: "Stage 3 plus failure of an adequate trial of a monoamine oxidase inhibitor"

Stage 5: "Stage 4 plus failure of an adequate course of electroconvulsive therapy"

2.6 Repetitive Transcranial Magnetic Stimulation

rTMS is a non-invasive procedure in which cerebral electrical activity is influenced by a rapidly changing magnetic field[22]. The magnetic field is created by a plastic-encased coil which is placed over the patient's scalp. The magnetic field can be directed onto specific areas of the brain. rTMS can modulate cerebral activity by low or high frequencies. In contrast to ECT, rTMS can induce cortical electrical activity without causing a seizure; it is sub-convulsive and therefore does not require anaesthesia[10]. The term "repetitive" is used to indicate the fact that the magnetic stimulation is delivered at regular intervals. rTMS therapy was approved by Health Canada for clinical delivery in Canada in 2002. Currently, two companies have multiple machines licensed for use in Canada. [22].

2.6.1 Target Populations

Clinicians interviewed recognize that TRD patients are the primary target population for rTMS, but suggested that a secondary market might be people who are strongly averse to taking medication. There is also a group of people for whom cognitive behavioural therapy does not work, as it does require substantial time and mental effort. Clinicians interviewed identified some other potential patient subgroups for which current treatments (i.e., anti-depressant medications and/or ECT) are problematic, because of potential side effects, for which rTMS could be a useful option including children and adolescents, pregnant women, women with postpartum depression, and individuals with medical conditions (e.g., some cardiac conditions) that rule out ECT. For a more in-depth description, please refer to section 3.3.4.1 in this report.

2.6.2 Contraindications for use of Technology

Absolute contraindications to rTMS include the presence of metallic hardware in the head and neck such as aneurysm clips, cranial implants, brain stimulators or electrodes or any other devices made of ferromagnetic material in the head with the exception of the mouth[26]. Increased intracranial pressure, epilepsy or history of seizures, severe cardiovascular disease, cardiac pacemakers, implanted medication pumps, intracardiac lines, and medications that lower the seizure threshold are also contraindicated[26].

3 Social Context

Summary of Social Context Findings:

- *rTMS is currently being provided to adults with treatment resistant depression at two locations in Alberta, the Centennial Centre in Ponoka (funded publicly) and the Riverview Medical Clinic in Calgary (funded privately). Youth and young adults can access rTMS at the Alberta Children's Hospital in the context of research.*
- *There is inequitable access to rTMS, and mental health programs in general, across the province*
- *Experts in Alberta believe that rTMS should be considered as one treatment option as part of the overall care pathway for people in Alberta with treatment resistant depression; rTMS should be considered after medications and cognitive behavioural therapy but before electroconvulsive therapy*
- *There is likely capacity to deliver rTMS in Alberta. However, no reliable estimate of demand could be provided.*

3.1 Research Objective

To understand the Alberta experience with rTMS to date and to determine the burden of illness, patterns of care and capacity in Alberta as it relates to using rTMS for the treatment of MDD.

3.2 Methods

Key informant interviews were conducted to collect information to describe the current social context in Alberta. Ten telephone interviews were conducted with twelve key informants[1] between September and October 2013, ranging in length from 25-90 minutes. The interview participants included seven members of the rTMS Expert Advisory Group and five additional individuals identified through a snowball sampling method as having a valuable perspective to inform the policy question. The participants included individuals working in Edmonton, Calgary, Ponoka and Grande Prairie and had a range of health care experience (five psychiatrists, one social worker, one psychologist, one neurologist, one researcher with a neurobiology background, and three with a mental health nursing background).

A semi-structured interview guide was developed to guide the interviews. This guide evolved over the course of the interviews, as questions were refined to reflect what had been learned through the previous interview(s). All

[1] One interview was done with a group of three individuals.

of the interviews were audiotaped with the consent of the interview participants and detailed notes were taken. Using the qualitative analysis method of constant comparative analysis, the notes were reviewed with the purpose of identifying key themes related to the policy questions being posed.

3.3 Findings

3.3.1 Treatment resistant depression in Alberta

3.3.1.1 How many Alberta psychiatrists would be treating people with treatment resistant depression?

MDD (particularly TRD) is a large proportion of the caseload of most psychiatrists. Many psychiatrists do not see people with depression unless they have failed to respond to initial treatments provided through Employee Assistant Programs (EAP), family physicians, and/or community psychologists. As such, EAP and primary care practitioners provide much of the frontline treatment for individuals with depression, and psychiatrists see a high number of patients with severe TRD.

3.3.1.2 What is the burden of illness?

One informant noted that depression is one of the most burdensome illnesses in Canada, and the leading cause of occupational disability in Canada; Alberta is no exception[27]. Many of the clinicians interviewed corroborated this perspective stating that the burden of illness in society was very high; it affects a large number of people, has a large impact on their ability to function in their life and impacts their families' lives. One clinician stated that if you were listening to the "water-cooler conversation" in mental health right now, the huge issues are stigma and the increasing prevalence of depression and anxiety. Much of depression and anxiety is currently not being treated or not being optimally treated. In addition, the burden of illness is large in youth. One clinician noted that there has been a shift towards non-institutional treatment for severe and chronic psychiatric illnesses, which has been accompanied by recognition of potentially harmful effects ('burden') upon the patient and the patient's caregivers.

Other informants expressed concern about the potential for over-diagnosing MDD. As one clinician stated*:*
"The DSM diagnostic criteria used for depression, while perhaps the "best" available, are quite subjective and may be biased toward over diagnoses. Additionally, the absence of etiology in the criteria, and the lack of a demonstrable and treatable pathophysiological process in the clinical setting, make approaches to treatment difficult to plan; especially where social issues or substance abuse aren't easily identified. The various treatments available generally do help but determining individual response in advance of treatment in the clinical context is a big problem."

3.3.2 Current treatment options for treatment resistant depression

3.3.2.1 Electroconvulsive therapy

For people not responding to medications and/or talk therapy (i.e., people with TRD that is severely affecting their ability to function), ECT is currently the only option. ECT is acknowledged by many of the key informants interviewed as the most effective treatment for TRD; a view supported by the CANMAT guidelines[28]. One clinician interviewed who was very knowledgeable about ECT stated that in his experience almost all people with TRD respond positively to ECT. Many people are enthusiastic about ECT because it works so well for them and they do not experience any significant side effects, stating that: *"Comments about ECT and cognitive side effects refer mostly to older forms of ECT. Modern ECT is well orchestrated and safe. In 8 to 10 minutes from entering the treatment room they have had the treatment successfully under anaesthetic and are in the recovery room."*

There are a number of barriers, however, that prevent ECT from becoming the treatment of choice:

I. ECT is highly stigmatized, even among health care staff. As a result many individuals are highly resistant to trying this option and many health professionals are reluctant to recommend ECT to their patients, primarily because of the possible side effects of ECT related to memory and cognition. A number of psychiatrists in Northern Alberta, for example, question the efficacy of ECT. They are also concerned that the potential side effects (e.g., impairment to memory and cognition) may outweigh the effectiveness. This is despite the fact that *"ECT meets level one evidence criteria for acute efficacy, relapse prevention, and safety and tolerability."*

II. ECT requires special equipment, a psychiatrist willing and trained to provide ECT, a general anesthetic and anesthesiologist, and in some facilities operating rooms – all scarce resources.

III. The first trial of ECT is done on an inpatient basis making it necessary for the person to be admitted to hospital. There are many people living in the community with severe TRD that will not get access to an inpatient bed. Subsequent maintenance ECT treatments can be done on an outpatient basis.

IV. Current access to outpatient ECT is a challenge. As one key informant noted: *"Operating room (OR) time is scarce and outpatients don't tend to show up a certain % of the time, and that's frustrating for the OR people."*

Currently, ECT is provided in most hospitals across the province with mental health beds. Access is limited in Northern Alberta; ECT is only available in Grande Prairie, where one psychiatrist is providing ECT. As of September 2013, ECT was not being provided in Fort McMurray. Access to ECT is particularly difficult for people living in areas far from a site that provides ECT, as they may require an overnight stay as an inpatient due to the length of travel time from their home. For these patients, bed capacity issues affect their ability to access ECT treatment. Overall, there seems to be a large number of people with TRD across the province who could potentially benefit from ECT but will not consider it as a treatment option and/or do not have access to it. In addition, a number of the interviewees wondered what portion of the population with TRD could be managed better earlier on (i.e., if more treatment was available, and there was less stigma, etc.), before they became treatment resistant. A strong influencing factor is an overall lack of access to publicly funded mental health programs and professionals.

3.3.2.2 Promising treatments on the horizon for people with treatment resistant depression

The key informants interviewed noted that there they were not aware of many emerging treatments for TRD. A few interviewees described being interested in emerging technologies for people who are depressed, and for other psychiatric disorders; most technologies involved some form of brain stimulation (e.g., implantable devices that provide deep brain stimulation; vagal nerve stimulation; low dose transcranial direct stimulation). Even with rTMS, which has the strongest evidence base, there is ongoing debate about treatment parameters.

There has not been any recent revolution in anti-psychotic medications. There had been great hope that through the human genome project more targeted treatments for particular types of depression might be developed, but so far few have been developed. However, much more research is underway. The main advances have come in the area of psychological treatments such as cognitive behavioural therapy, and in trying to make these treatments more available to people with depression. There have been incremental advances in Alberta with respect to this. Currently in Alberta, many people with depression have to pay a private psychologist to obtain cognitive behavioural therapy.

3.3.2.3 Access to treatment in northern Alberta

Access to mental health services in Northern Alberta can be particularly difficult because of the long distances that people have to travel. There are some traveling psychiatrists who visit smaller communities, and this has worked well to improve access in some areas. These psychiatrists often do the initial diagnoses and assessment, start treatment and then follow patients for a short period of time. Once an effective medication has been found and the patient is improving they will often be referred back to their family doctor for ongoing monitoring and

care. People often do not want to travel to Edmonton for services such as ECT, meaning that it is important to be able to provide treatment options in the North. Refer to **Appendix A** for a high-level overview of mental health service delivery in the North. A more in-depth environmental scan would need to be conducted in order to determine access to treatment across Alberta, including the eastern and southwestern parts of the province.

3.3.3 Access to repetitive transcranial magnetic stimulation for treatment resistant depression and current practice in Alberta and Canada

Two sites in Alberta provide rTMS to adults with TRD, one publically funded service located at the Centennial Centre in Ponoka and one privately funded service at a psychiatry clinic in Calgary. Both sites provide patients with an initial course of treatment of four weeks in duration, and continue to provide maintenance rTMS treatment to many of their patients. Treatment is provided to patients with both unipolar and bipolar depression.

rTMS is not widely provided across Alberta at this time, so there are issues with equity of access. The clinicians providing rTMS noted that people referred for rTMS are often resourceful individuals who know the literature and seek out the treatment themselves. These people are often more aware of and are actively researching treatments. They will often go to their family doctor, or psychiatrist, and ask to be referred for rTMS treatment.

With respect to access to rTMS for children and young adults, there is one clinical trial underway at the Alberta Children's Hospital that is exploring the effectiveness of rTMS for treatment resistant MDD in adolescents. A brief description of all three sites is outlined below.

3.3.3.1 Centennial Centre in Ponoka (publicly funded service)

Centennial Centre began providing rTMS about 10 years ago, initially targeting TRD on a compassionate basis because of the lack of conclusive research on clinical effectiveness at the time. To date, they have not widely advertised the availability of rTMS treatment, as they have been waiting for the development of the evidence base. Before setting up this rTMS clinic, the psychiatrist providing the treatment went and spent a week in Hamilton with Dr. Gary Hasey, a clinician-researcher with rTMS experience. There is no cost to patients to receive rTMS treatment at this location. The majority of referrals come from Calgary, Edmonton and Central Alberta.

3.3.3.2 Riverview Medical Clinic in Calgary (private service)

The Riverview Medical Clinic in Calgary began providing rTMS to patients early in 2012, as it was felt there was a need for this treatment option in Calgary. To date referrals have been for patients who are very treatment resistant and have come from both psychiatrists and family physicians. Patients initiate many of these referrals

themselves, often discussing it with their own psychiatrist or family physician and asking for a referral for rTMS treatment. As of September 2013 this clinic had treated 32 patients, 12 males and 20 females, with both unipolar (or MDD) and bipolar depression. Over half the patients treated to date have been bipolar. They have also treated two patients with depression with psychotic features, and one case of conversion disorder with depression. Some of these patients had not responded well to ECT but did respond positively to rTMS. More than half of this initial group of 32 patients is still receiving maintenance rTMS. To date, there has been little research on using rTMS for maintenance, although one recent study showed that a follow-up maintenance session improved remission rates.

3.3.3.3 Alberta Children's Hospital research project for adolescents with treatment resistant depression (publicly funded clinical trial)

The current research being led by Dr. Frank MacMaster and Dr. Adam Kirton at the Alberta Children's Hospital in Calgary is an open label trial. They want to give young people (age 12-22) with TRD an opportunity to try rTMS as a treatment. Dr. MacMaster's interest is in the imaging, and he is doing research on how the brain's physiology changes as a result of the rTMS treatment. There is limited research on the use of rTMS for depression in adolescents (see section 6), so this research will be a valuable contribution to this knowledge base.

3.3.3.4 Treatment protocols currently in place at the three Alberta sites

The treatment protocols in place at the three sites where rTMS is currently being provided in Alberta have been summarized below in **Table 1**.

Table 1: Repetitive transcranial magnetic stimulation treatment protocols in Alberta

rTMS Location	rTMS session length (minutes)	Stimulation time (minutes)	Number and frequency of rTMS sessions (for initial course)	Stimulation frequency and duration	Area of the brain stimulated
Centennial Mental Health & Brain Injury Centre (Ponoka)	30	10-20	Monday-Friday 4 weeks (20 sessions)	Left-sided fast (10 hertz), or right-sided slow (1 hertz) (rapid – 25 x 50 pulse trains with 30 seconds rest; slow - 4 to 7 x 120 pulse train with 3 minutes rest)	Right or left, dorsal-lateral, pre-frontal cortex
Riverview Medical Clinic (Calgary)	60	40-50	Monday-Friday 4 weeks (20 sessions)	20 hertz (40 trains of pulses)	Left dorsal-lateral, pre-frontal cortex
Alberta Children's Hospital clinical trial research protocol – adolescents (Calgary)	50-60	37.5	Monday-Friday 3 weeks (15 sessions)	10 hertz (75 trains of pulses/3000 pulses)	Left dorsal-lateral, pre-frontal cortex

rTMS Repetitive Transcranial Magnetic Stimulation

The protocols in use at the Riverview Medical Clinic and by the Alberta Children's Hospital research team are similar. Both stimulate the left dorsal-lateral, pre-frontal cortex (DLPFC) using high frequencies; Riverview Medical Clinic is using a slightly higher frequency of 20 hertz. The Centennial Mental Health and Brain Injury Center (Centennial Centre) uses this type of protocol for some patients, but in some patients they stimulate the right DLPFC using low frequencies. Both the Centennial Centre's and Riverview Medical Clinic's treatment series are 20 days (i.e., Monday to Friday) over four weeks, in comparison with the trial at the Alberta Children's Hospital where treatment is provided for fifteen days over three weeks. At both the Centennial Centre and the Riverview Medical Clinic, maintenance treatment is being provided. Over time they have learned that what appears to be most effective is to begin with weekly maintenance treatments and then slowly wean back from that based on clinical symptoms and patients' descriptions of their functioning. All three sites have found that the treatment protocols they used are well tolerated and safe, with the biggest issue being the initial treatment phase where people need to come daily for treatment over a number of weeks. When people are still very depressed, this may require a lot of commitment from the patients' families.

3.3.3.5 Costs to patients for repetitive transcranial magnetic stimulation treatment in Alberta

There is no cost to patients participating in the Alberta Children's Hospital clinical trial, or to patients being treated at the Centennial Centre; both are funded through public dollars. At the Riverview Medical Clinic in Calgary, the cost to patients for an initial 4-week course of treatment (20 sessions), with everything included, is $5000. The cost for maintenance treatments is $250/session. To date rTMS for TRD is not covered by most private medical insurance plans.

The key informants interviewed have some knowledge of the current status of the use of rTMS for TRD in other parts of Canada. rTMS has been an approved treatment for TRD in Canada since 2002, and was first used to treat mood disorders in 1994. Currently, both Saskatchewan and Quebec cover rTMS therapy. Toronto (Centre for Addiction and Mental Health) and Montreal (Douglas Mental Health University Institute) have very well established brain stimulation centers where patients with depression are being treated. Key informants suggested that there may be a lot to learn from these centers, if the decision is made to publicly fund rTMS treatment for TRD here in Alberta.

3.3.4 Clinician experience with repetitive transcranial magnetic stimulation in Alberta

Overall, the sense among those interviewed is that the psychiatry community is becoming more aware and accepting of rTMS as a treatment option for TRD. One clinician described the current situation as moving from *"a small number of accepters with the vast majority being highly skeptical, to a general acceptance of it as a*

usual technique." Another clinician noted that there has been talk amongst the psychiatrists and psychologists about rTMS (due to profiling on the Alberta Health Services website); this clinician had a general impression that psychiatrists and psychologists were open to using it for TRD treatment. According to one key informant, psychiatrists in northern Alberta have no or very little direct experience referring patients for rTMS as there is no treatment provided north of Ponoka. This may also be true of clinicians in other rural areas of the province. The impression is that rTMS is a new, promising treatment, and that Calgary has been doing the local research.

3.3.4.1 Patient populations for which repetitive transcranial magnetic stimulation is potentially an effective treatment

Clinicians described a number of patient subgroups for which current treatments (i.e., anti-depressant medications and/or ECT) are problematic, because of potential side effects, and for which rTMS could potentially be a useful option. These include:

I. *Children and adolescents*. Medication side-effects profiles are not good in youth, and ECT is not commonly used with young people, meaning that families are trying to find other options. One researcher stated that the response to medications and/or cognitive behavioural therapy in youth is about 50%, making rTMS of interest for this population.

II. *Pregnant women and women with postpartum depression*. Postpartum depression is known to start during pregnancy, so the earlier you can intervene during pregnancy the better the outcomes. rTMS may be of particular interest in this population of patients due to many women's concerns about taking medications during pregnancy.

III. *Individuals for which cognitive behavioural therapy is not a good option*. As one clinician notes, there is also a group of people for whom cognitive behavioural therapy does not work.

IV. *Individuals with medical conditions* (e.g., some cardiac conditions) that rule out ECT. As one clinician stated: *"rTMS would be an option for persons who are unable to have ECT, for persons who do not want to have ECT, for persons for whom ECT was not adequately effective or simply not effective."*

Alberta clinicians with experience providing rTMS said it is difficult to determine whether there are particular groups of people who respond better to rTMS. One interviewee said that in conversation with a world renowned expert, he suggested that patients with bipolar depression may respond more quickly to rTMS than patients with unipolar depression. Some Alberta-based rTMS providers' experiences to date suggests that people who are younger (i.e. ages 18 to 30 years old) seem to have less of a need for maintenance rTMS treatment. If this is true, rTMS may be particularly beneficial for younger patients. Key informants expressed some uncertainly

regarding whether elderly people responded as well as younger people to rTMS. Based on local practice experience to date, if the individual has been depressed for less than six months the chances of responding to rTMS are higher.

Clinicians recognize that TRD is the primary market for rTMS, but suggested that a secondary market might be first cases and/or people who are more apt to undergo treatment rather than take medication; these are two additional groups of people, then, to consider expanding the treatment to at some point. This area of particular patient subgroups for which rTMS might be a particularly useful treatment was described as important area to explore through the systematic literature review component of this HTA, and through future research.

3.3.4.2 The use of repetitive transcranial magnetic stimulation outlined in clinical practice guidelines and/or incorporated into clinical care pathways for depression

The majority of the clinicians interviewed were not aware of whether the use of rTMS had been incorporated into updated clinical practice guidelines on depression. The guidelines that psychiatrists in Alberta widely use are the CANMAT guidelines as they have a sequential, stepped approach. CANMAT Guidelines for neuro-stimulation therapies state that rTMS is second line with level 1 evidence for acute efficacy, safety and tolerability and Level 3 evidence for relapse prevention[28]. Other guidelines that were referred to include the consensus guidelines from the American Psychiatric Association and the Canadian Psychiatric Association position papers. The perception of researcher-clinicians was that the literature on rTMS has now gone through its growing pains; more specifically that systematic reviews are able to say that it works better than placebo, but perhaps not in truly TRD cases and that it seems to be a safe and acceptable treatment for depression. They also felt that it is not going to replace ECT, which they described as being a very effective treatment for TRD[29]. An *"Achilles heel of ECT"* is that although it works there is a high relapse rate, so some people end up requiring maintenance therapy (which may involve getting ECT as an outpatient once every couple of weeks).

There are no local depression care pathways that incorporate the use of rTMS. One clinician-researcher noted that NICE has a good pathway that is very detailed. At this point rTMS is only recommended for research purposes, due to uncertainty in clinical efficacy[30]. Recently, Alberta Health Services Addictions and Mental Health Strategic Clinical Network has developed a Clinical Pathway for Adult Depression Protocol. This draft document is a collection of the currently agreed best practice evidence for the identification, assessment, treatment and follow-up of adults with suspected depression, aged 18-65 years, in primary care and community care settings. rTMS is not described as a treatment option in this document, likely in part because this document

does not cover specific treatments for TRD, but rather recommends a psychiatric consult. ECT is also not covered in this document.

Clinicians did describe where they thought rTMS might fit in a care pathway for TRD, with most clinicians saying it would probably fit after medications and cognitive behavioural therapy but before ECT. rTMS was described as *"the in-between step."* Some clinicians actively providing rTMS said it was very challenging to determine where it might fit in a clinical care pathway, based on their understanding of the research and their experience to date. As indicated above, it may be optimal to intervene early on in the TRD trajectory, as people may respond better and require fewer rTMS treatments. More research is required to answer this question.

3.3.4.3 Potential size of the patient population

No key informants were able to say what percentage of people with TRD might be candidates for rTMS if it were more widely available in Alberta, in part because it has not been available. Considering the educated guess of the prevalence of TRD in Alberta being approximately 28,000, if even 5% of these individuals were candidates for rTMS this would amount to 1400 individuals. As noted above, people who may be particularly good candidates for rTMS include pregnant women and women with post-partum depression, young people, people more recently diagnosed with TRD, and people with bipolar depression.

One psychiatrist who gets many referrals of patients with TRD was asked which patients he would discuss rTMS with as a possible treatment option. His experience to date is with patients with severe TRD who have been referred to him to discuss ECT as an option. Not everyone is willing to try ECT, however, and it is primarily this group of people who he would refer for rTMS. He gave the example of a man who is a farmer who comes down to see him regularly, and is so severely depressed that he is unable to function. Yet his family does not want him to have ECT. If rTMS or some other technology were an option, he would be an ideal candidate to try it. It is people like this patient, and a desire to offer other treatment for people like this – knowing that it will not work for everyone – that makes this psychiatrist interested in rTMS.

3.3.4.4 The usefulness of repetitive transcranial magnetic stimulation as a treatment for patients with treatment resistant depression

Clinicians actively involved in providing rTMS either as part of a research project or for clinical treatment were asked about their perspectives, based on their experience, of the usefulness of rTMS as a treatment for patients with TRD. Both the Centennial Centre in Ponoka and the Riverview Medical Clinic in Calgary have experienced some success in treating both unipolar and bipolar depression with rTMS. At Centennial Centre,

approximately 2/3 of the patients treated achieve some degree of improvement (i.e., mild, moderate or marked), and 1/3 sees no improvement. Most often they would see a degree of improvement, rather than complete remission, although occasionally, patients do experience a complete remission. Usually patients require maintenance treatment once per week initially, and then at less frequent intervals until they do not need it anymore. Their experience is that the majority of people who need maintenance seem to need it for a long time; they have had people coming back for more than five years.

Experience to date through the Alberta Children's Hospital clinical trial has been that there are noticeable changes over the three weeks of treatment for the 2/3 of young people that have responded to rTMS. As one of the researchers stated: *"we have some kids who start the trial barely moving or talking (and some have struggled for years), and then they're joking and talking by the end of the trial. Parents are so happy to "have their kid back"*. Experience at the Riverview Medical Clinic to date has also been quite positive. Their outcomes to date include a response rate of 79% with 50% of their patients achieving remission after 20 treatments. Note that more specific data can be provided upon request.

3.3.5 Perspectives on the patient experience with repetitive transcranial magnetic stimulation

Clinicians and researchers providing rTMS treatment report that the patients (and/or their family members) they have treated to date tend to have a higher socioeconomic status, and in particular are frequently well educated. They are often actively seeking out alternative treatments for TRD, and have often tried many treatments before. So the current experience here in Alberta is that patients come to an rTMS provider having researched the treatment themselves. One psychiatrist said that his experience trying to recommend rTMS to patients who have not previously heard of it (either through the media, their own research, and/or someone they know and trust) are reluctant to because to them it *"just sounds crazy".* Both clinics said that media profiling of the treatment (e.g. the Dr. Oz show) helps to increase the profile and acceptability of, and the interest in, the treatment. In the Alberta Children's Hospital clinical trial to date, the recruitment rate has been high, as people are out of alternatives and really want to try something else. Teens also tend not to like medication because of the side effects.

For those patients who try rTMS, the treatment is generally well tolerated. All rTMS providers said that the treatment can be perceived to be a little bit uncomfortable, primarily in the first two sessions. There is good tolerability and this improves over time. Part of the Alberta Children's Hospital clinical trial involves assessing tolerability; they do a lot of education beforehand and have made a YouTube video so that young people coming in know how it will work. The mapping part of the process gives them an introduction to what the

rTMS will feel like. "*Kids fill out standard tolerability measures, and they re-measure them once per week during the trial."* For youth with co-morbid anxiety, this does present a patient management issue, but it is not unlike what it would be for any kind of treatment. One benefit of rTMS is that it is a structured treatment. Once a patient has done it once, they know what to expect for the rest of the treatments. There has been one dropout to date in the Alberta Children's Hospital's clinical trial, as a result of co-morbid anxiety, so in patients with extreme anxiety this can still be an issue. To date there have been no drop-outs at the Riverview Medical Clinic due to anxiety; they also spend considerable time upfront teaching patients about what rTMS is, the theory underlying how it works, and what to expect during the treatment sessions.

No serious side effects were noted by those interviewed. One researcher noted that unlike ECT, where there can be negative effects on cognition, it is the cognitive symptoms related to depression that may be most positively affected by rTMS. To date, in the Alberta Children's Hospital clinical trial, the impact on cognition has only been positive. One clinician providing rTMS to adults noted that the odd time a person has a lot of pain, but that means that the setting needs to be recalibrated and the protocol needs to be changed, as the treatment should not be painful. The biggest stress is coming in five days week for 3-4 weeks for the initial course of treatment. This is a big commitment for patients and their families, and is likely the most difficult barrier to navigate. One clinician noted that patients whose depression is decreasing can get increased mood instability for a period of time. This is in part because changes that would usually take weeks can take days. *"People can become fragile when they are rapidly induced into wellness."*

3.3.6 Capacity for providing repetitive transcranial magnetic stimulation in Alberta

Given the lack of certainty regarding what the demand for rTMS might be, it is not possible to determine whether Alberta Health has the current capacity to support this volume of service. Right now there is an obvious lack of treatment in the northern half of the province, as the furthest north rTMS is currently available is Ponoka. Whether there are enough psychiatrists in Alberta who might have the time and interest to provide rTMS, since the treatment needs to be overseen by a psychiatrist, is also a complicated question to answer at this time. As one clinician noted, statistically Edmonton has enough or more than enough psychiatrists right now, Calgary has about the right number, and the rest of the province is desperate. Some clinicians felt that rTMS could be provided in many centers across the province. One clinician stated: *"If you know something about neuro-science it's pretty straightforward. You would just need some training to get familiar with the particular machine. Need to have the right safety protocols in place (e.g., in case patients might have a seizure). So anywhere there is ECT suite you could easily offer rTMS."*

Regarding building capacity to provide the treatment, clinicians currently overseeing or directly providing rTMS treatment said that there is a bit of a learning curve, but it is not an overly difficult treatment to learn. The psychiatrist overseeing the treatment needs to be interested in reading the literature, aware of the principles of TRD, and somewhat familiar with ECT. As mentioned above, the psychiatrists currently overseeing rTMS treatment of adults in Alberta completed the required training over a weeklong period, and are committed to ongoing learning and reading the published research on rTMS.

To train people to do the procedure, there is a certain level of diligence and technical ability required to set up and execute the procedure. As long as there is appropriate medical coverage, nurses (Registered Nurses or Licensed Practical Nurses) or research associates (if it is a research project) can be properly trained to do the procedure. At the Riverview Medical Clinic, all of the nurses providing rTMS must be Registered Nurses because they are providing direct patient care under the direction of a psychiatrist. In accordance with the Alberta Health Professions Act, persons providing direct care must be a member of a regulated health profession. One clinic described the importance of looking for nurses with astute clinical observation skills.

The Riverview Medical Clinic has gone through this experience quite recently (i.e., in the past 2 years). They described their experience as follows:

I. Although the actual rTMS treatment is delivered by a trained nurse, the initial landmark mapping (i.e., to ensure that the area to be stimulated is precisely determined) and the determination of the initial motor threshold are a physician's responsibilities.
II. The nurses providing the treatment are trained in the clinic, with the training including:
    a. How rTMS works, including some neuroanatomy and neurophysiology;
    b. How to operate the machine;
    c. Landmark-mapping;
    d. Checking motor thresholds; and,
    e. Patient teaching and patient assessment.
III. Once the machine was purchased, two psychiatrists and the nurse manager of the clinic attended an intensive week-long course put on by the Berenson-Allen Centre for non-invasive brain stimulation at Harvard. This 5-day course included intensive theory and practice, and was developed based on current research. Faculty included: Alvaro Pascual-Leone, MD, PhD, Professor of Neurology at Harvard

Medical School.[2] They also participated in some initial training with Dr. Gary Hasey in Hamilton Ontario.

3.3.6.1 The cost of a repetitive transcranial magnetic stimulation device, and other associated costs of providing rTMS treatment

The Riverview Medical Clinic in Calgary has the most recent experience of setting up an rTMS clinic, including the purchasing of equipment. Their Magstim machine cost $80,000 and they paid an import tax of ~$5000 as it was purchased in the United Kingdom. To date the maintenance cost of the equipment has been very low. A one-week shutdown was required when the magnet was sent for maintenance. Patients sit in a reclining chair that was purchased at the Brick. Lycra swimming caps are used to do the landmark mapping. Other supplies required include: earplugs, tape measures, and emergency response equipment (i.e., rebreathing mask, syringe and needles, first aid supplies).

3.3.6.2 Increasing awareness of and knowledge about repetitive transcranial magnetic stimulation

Given the prevalence of TRD, and its impact on quality of life, it is important that health professionals (e.g., social workers, psychologists, family physicians, psychiatrists) know the types of treatments that patients with TRD have the potential to access, so that appropriate referrals can be made. Although most practicing psychiatrists would be aware of rTMS, most would have no direct experience with referring patients for rTMS – primarily because of the lack of access to rTMS currently in Alberta. For psychiatrists, like for many practice changes, the knowledge translation/transfer (KT) piece was acknowledged as being very important. There is currently a lack of awareness of rTMS among other health professionals working with clients with TRD. If the decision is made to publicly fund TRD, then spreading the word will be important. One key informant noted that: *"the messaging needs to be spread very broadly across many healthcare provider roles and disciplines, given the common nature of these mental health conditions."*

Alberta Health Services Health Professionals Strategy and Practice (HPSP) could participate in developing resources and tools to increase understanding of rTMS and where it fits in the care pathway. HPSP has learned a lot about communicating with social workers, psychologist and other allied health professionals. Any implementation plan needs to have two to three different kinds of outreach, including through the executive

[2] Note that this is a CME course run in conjunction with Harvard Medical School

directors for mental health in each zone and through the zone senior leaders. HPSP also have list serves developed for all the disciplines. There are a large number of psychologists working in mental health, so information about rTMS could be distributed via the psychologist list serve. Sending out information through list serves would also work well for many other health disciplines, including social workers. Pre-packaged information might also be distributed via regulatory colleges through their newsletters and other material they send out to their members.

With respect to social workers, messaging will be required across Alberta Health Services and potentially across the many departments where social workers practice (e.g., medicine, surgery, chronic disease programs, cardiac, emergency). Another avenue that may work would be to bring information to the provincial social work discipline council, and they could in turn have the zone councils bring it to their mental representatives to distribute. They also have a number of networks established through which they could distribute information, including through the Addictions and Mental Health Strategic Clinical Network. In addition social workers also practice in other sectors (e.g., municipal governments; other government agencies) where they may come across clients living with TRD. As one key informant stated: *"social workers, along with family physicians, are often the 1st responders' to a range of social, emotional, psychological and mental health issues requiring screening and referral, meaning that broad messaging to disciplines and care providers (in and outside of mental health programs) can increase awareness, potential referrals and in turn, help address stigma by bringing the topic forward."*

3.3.6.3 Perspectives on providing repetitive transcranial magnetic stimulation as an insured service in Alberta

All the key informants interviewed were asked their perspective on whether rTMS should be provided as an insured service in Alberta. Those people with direct experience providing rTMS, and/or with heavy caseloads of patients with TRD, were positive about including rTMS in the care pathway for people with TRD in Alberta. Their view was that when there is an effective means of treating a mental health disorder, then it should be accessible without paying out-of-pocket.

Most key informants could not see any negative consequences for publically funding rTMS. They truly hoped that the body of evidence was strong enough to show that rTMS was effective for this patient population. One reason for this is the reality that there will always be barriers to accessing ECT so it is often not a very practical option, even if it is effective. rTMS resolves a lot of those issues, and for some groups of people ECT is not

even an option. For people who have some inhibition to trying ECT, for whatever reason, then there is another option to try; *"rTMS is just so much more acceptable to people".*

Key informants more familiar with the recent research on rTMS state that there is an increasingly strong evidence base, both clinical and neurobiological, for the effectiveness of rTMS in adults. We know that it both decreases depression in people with TRD and we know how it affects the brain or the mechanism of treatment. In addition, some key informants thought that as the evidence starts to accumulate we should not be too far off providing this as a treatment option for adolescents as well. One interviewee noted that rTMS has more evidence already than a lot mental health treatments currently provided in healthcare system.

The main challenge was thought to be the logistics of providing access to rTMS; that is, ensuring that the right equipment is in the right spots with the right people to provide it, and that the right people know it is there as an option to discuss with their patients. This highlights the importance of developing a good communications and knowledge translation strategy. Some people had suggestions about how rTMS might be provided in Alberta, which are briefly described here.

One key informant felt that proper non-invasive brain stimulation centers that are publicly supported need to be built, in part because the research is still rapidly evolving, as well as, to fine-tune treatment protocols and the technology, and to explore the use of rTMS for other mental health and neurological disorders. Given this, it may make sense to establish public centers that use rTMS for a variety of neurological disorders, not just TRD. There is apparently no shortage of good people with interest in neuro-modulation and brain stimulation, so there is lots of potential here. There was some hope that perhaps clinical practice and research can move these things forward together. Others expressed concern with this type of model, however, as community-based treatment distributed across the province may provide better access for individuals with TRD.

A key informant working in Northern Alberta described some of the unique challenges to serving their patient population. Treatment for people living in the North might require special consideration. A mental health professional working in the North said that if rTMS was available only in Edmonton, he knows from past experience that physicians would experience a great deal of difficulty getting people to consider going to Edmonton for the treatment. In general strong family support is required to get depressed people into treatment and rTMS would be no exception. This means in order to increase capacity for rTMS in the North, ideally services should be provided across the North. Given the reality that rTMS needs to be provided daily for a

number of weeks, this mental health professional wondered whether one option to consider might be to equip a number of clinics across the North with the equipment, and have the treatment provided by a traveling team.

Other key informants provided a more cautionary perspective. An important contextual issue here is that historically people with mental health problems have been exposed to treatment before it has been well researched. This historical issue cuts across all treatments but concerns are higher with treatment that is more invasive. There was also some concern expressed by a couple of key informants that there might be a massive shift in demand for rTMS if it is made available publicly, and therefore the potential for a lot of money being spent on this one treatment. These interviewees did pose a bigger question then, which is: Is this the best way to spend public dollars? They noted that related questions worthy of consideration include: What is known about health promotion and its impact on treatment needs later on, and should more resources be allocated to providing more people with better treatment sooner in their illness trajectory, rather than putting resources into TRD? One key informant stated, for example, quality cognitive behavioural therapy is not delivered very well in our current system, and this has the potential to help many people. Evidence-based psychotherapy is cost effective in that a variety of health professionals can be trained to do cognitive behavioural therapy and it can be done as group therapy. Cognitive behavioural therapy could be made accessible to many more people with a few salaried positions, but currently this is not a priority in the system. There is also some question about how many people are not being treated for depression, and/or simply do not adhere to treatment, and whether this leads to an increase in TRD. Some interviewees wondered if more support should be provided to help people adhere to treatment. If there is extra money to spend on mental health, perhaps it should be put towards evidence-based treatment for people living with depression before these individuals get to the point of being treatment resistant (e.g., provide good community-based care through primary care, and also a good intermediate level between primary care and tertiary psychiatry care).

There was an equally strong argument articulated by key informants that because of the burden of illness of TRD, providing another evidence-based option in addition to ECT for this population is very important. One key informant summed up this complex issue and his perspective as follows: *"Many persons have TRD. Of this group many are inadequately treated, have limited or no response to treatments or relapse quickly, have access and logistical hurdles to obtain treatment, or have personal feeling or beliefs that limit treatment. This directly costs the taxpayers of Alberta."*

3.3.7 Conclusions

In summary, depression is a major public health issue in Alberta, Canada, and internationally. The burden of illness is high; people with depression suffer deeply and it pervades all areas of their life. Cognitive behavioural therapy and medication are effective when available, appropriately utilized, and the person's neurobiology responds well. Yet there are still far too many people in Alberta suffering because treatment is not available, not used appropriately, or the person's neurobiology does not respond. ECT is an effective treatment for those people who do not respond to these first line treatments. There are a number of barriers to accessing ECT, most of which are challenging to address. rTMS is considered a potentially promising treatment option for people with TRD because it can potentially be made more widely available than ECT, people seem to accept rTMS (i.e., as it does not have the same stigma attached to it), and there is evidence that it can improve the symptoms of depression.

Currently, rTMS is being provided to adults with TRD at two locations in Alberta, the Centennial Centre in Ponoka and the Riverview Medical Clinic in Calgary. The service at the Centennial Centre is provided at no cost to the patient. There is also a clinical trial with adolescents underway at Alberta Children's Hospital in Calgary. In all three settings, the health professionals involved have seen some success with rTMS for TRD, with approximately 2/3rds of patients responding positively to the treatment.

Key informants interviewed believe that rTMS should be considered as one treatment option and part of the overall care pathway for people in Alberta with TRD. There appears to be the capacity in Alberta to increase the availability of rTMS, should the decision be made to publicly fund it. rTMS can safely be provided in a community setting by registered nurses, with involvement of and oversight by a psychiatrist(s). Based on the experience of Alberta clinicians who are currently providing rTMS, the learning curve to develop and administer rTMS treatment protocols is not incredibly steep. Psychiatrists do need to have an interest in the technique and in keeping up with current literature, given the ongoing research being conducted to determine the most effective protocols.

Overall, the sense among the people interviewed is that the psychiatry community is becoming more aware and accepting of rTMS as a treatment option for TRD. Clinicians did describe where they thought rTMS might fit in a care pathway for TRD, with most clinicians saying it would probably fit after medications and cognitive behavioural therapy but before ECT. rTMS was described as *"the in-between step."* Developing and

implementing an effective knowledge translation plan was described as important should a decision be made to publicly fund rTMS in Alberta. Given the prevalence of TRD, and its impact on quality of life, it is important that health professionals working with individuals with TRD (e.g., social workers, psychologists, family physicians, psychiatrists) know the kinds of treatments that patients with TRD have the potential to access so that appropriate referrals can be made.

Finally, there was also a recommendation from many that, because of the high burden of illness and the current gaps in treatment, treatment for depression overall should be considered a high priority for mental health services planning in Alberta. That is, access to assessment and first line treatment for depression (i.e., psychotherapy, and in particular cognitive behavioural therapy; and anti-depressant medications) be more readily available across Alberta, with the intent of promoting mental health and decreasing the prevalence of TRD. Also, given what is known about the effectiveness of ECT for TRD, increasing access to ECT (including on an outpatient basis) should also be a priority.

4 Patient Experience with Repetitive Transcranial Magnetic Stimulation

Summary of Patient experience:

- *Literature on the patient experience with rTMS is limited (n=4)*
- *The experience of rTMS is generally positive*

4.1.1 Research Question

To determine the patient experience with rTMS

4.1.2 Methods

4.1.2.1 Literature Search

A systematic review of the qualitative literature was completed to describe the patient experience with rTMS. MEDLINE, EMBASE, PsychINFO, and CINAHL were searched from inception until May 30th, 2013. Terms aimed at capturing the target diagnosis, such as “depression,” “depressive disorder” and “depressed” were combined using the Boolean Operator “or.” These terms were then combined, using the Boolean Operator “and”, with terms describing the technology such as “trancranial magnetic stimulation” and “rtms.” Terms such as “interviews,” “grounded theory,” and “qualitative research” were used to narrow the results to include only

qualitative studies. Results were limited to humans and English language studies. Details of this search can be found in **Appendix B**.

4.1.2.2 Selection of Literature

All abstracts were screened in duplicate (GM and LS). Articles proceeded to full-text review if the study included only treatment resistant patients with major depressive disorder, looked at patient experiences with rTMS, reported relevant outcomes (see **Table 2**), had a qualitative research study design, and assessed at least one of the following: overall patient experience with rTMS, acceptability of the rTMS treatment process, tolerance of rTMS, or perceptions of patients and family members of treatment effectiveness (i.e., impact on depression symptoms, function, and quality of life).

Abstracts were excluded if they did not meet the criteria above, if the patients had other mood or anxiety disorders, or the study was only available as an abstract or poster. Abstracts selected for inclusion by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after abstract review proceeded to full-text review. As described above, studies were included if they met all inclusion criteria and failed to meet any of the criteria for exclusion presented in **Table 2**. For all studies, year of publication, country, patient selection, patient population, research methods and key findings were extracted using standardized data extraction forms. Discrepancies between reviewers during data extraction were resolved through consensus.

Table 2: Inclusion and Exclusion Criteria for Review of Patient Experience Literature

Inclusion Criteria	Exclusion Criteria
• Treatment Resistant patients (adults and children) with Major Depressive Disorder • Assesses at least one of the following: · Overall patient experience with rTMS · Acceptability of the rTMS treatment process · Tolerance of rTMS · Perceptions of patients and family members of treatment effectiveness (i.e., impact on depression symptoms, function, and quality of life) • Reports at least one of the following: · Duration of treatment · Whether hospital admission is a requirement · Experience during treatment (pain, negative sensations) · How well is the treatment tolerated · Public perception of treatment • Qualitative research study design	• Not Major Depressive Disorder, Treatment Resistant depression or depression • Not rTMS • Patients with other mood or anxiety disorders (e.g. bipolar, post-partum depression) • Studies without any reporting of patient experience, acceptability, tolerability, or perceptions of treatment • Studies reported only in abstract

4.1.3 Results

One hundred and twenty-nine abstracts were identified for review (see **Figure 1**). After abstract review, 99 were excluded. Thirty full text articles proceeded to full text review. Four articles met the final inclusion criteria. The findings from these four studies describing the patient experience with rTMS, from the perspective of the patient and/or their family, are narratively synthesized below. A high level summary of all four studies is provided in **Table 3** below.

Figure 1: Flow Chart of Studies Included in the Review of Patient Experiences

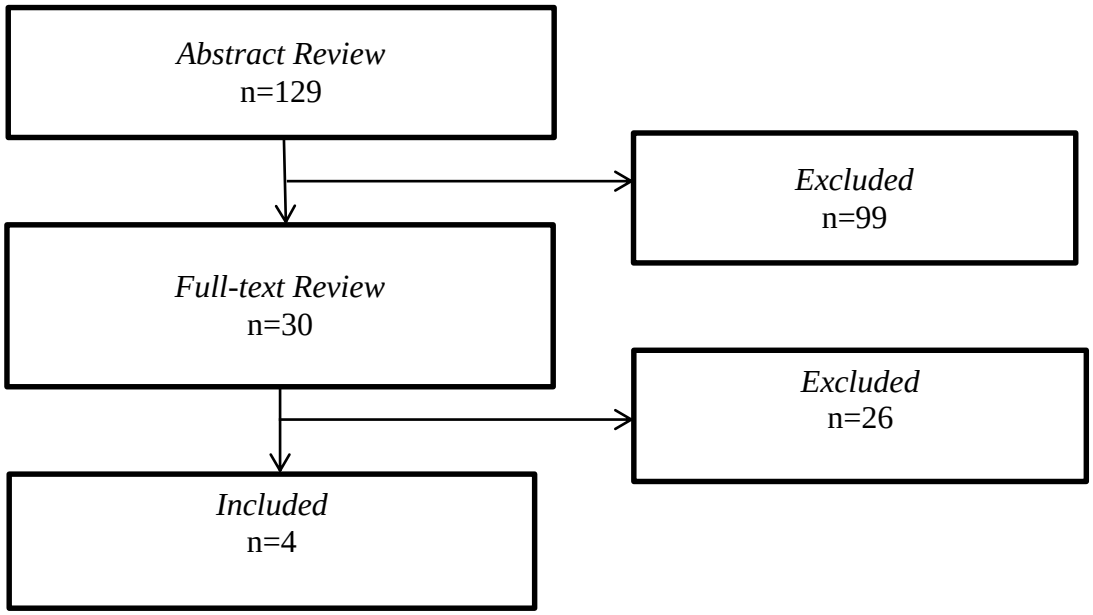


Table 3: Qualitative and survey research on the patient and family experience with rTMS

Author, Reference, Year of Publication, Country	*Patient Selection*	*Research methods*	*Key findings*
Kim[31] 2011, United States	**Patient Selection**: For Study 1, women attending their first prenatal visit between November 2008 and April 2009 at the University of Pennsylvania, were considered for inclusion. For Study 2, women attending their first prenatal visit in August 2009 at the University of Pennsylvania were considered for inclusion. **Inclusion Criteria:** None reported **Exclusion Criteria:** None reported **Patient Characteristics:** Study 1 included 460 pregnant women with a mean age of 24.84 (5.57) a mean gestational age of 17.12 (8.09) weeks and a mean score on the Edinburgh Depression Rating Scale of 8.19(5.89). Study 2 included 51 pregnant women with a mean age of 24.39(5.88), a mean gestational age of 16.82(8.25) weeks and a mean score on the Edinburgh Depression Rating Scale of 7.84(6.95).	**Study 1** – Pregnant women completed the Edinburgh Depression Rating Scale (EPDS), and a self-administered questionnaire on the acceptability of rTMS. **Study 2** - Pregnant women completed the Edinburgh Depression Rating Scale (EPDS), and a self-administered questionnaire on the acceptability of rTMS. These women viewed an informational video to increase their knowledge about TMS before they completed the acceptability survey.	Study 1: • The most acceptable treatment type was talk therapy with 43% responding that they would consider it. • 50.9% of subjects reported that they would not consider rTMS treatment • 48% reported that frequency of treatment would not deter them, 26% reported that treatment only once per week would be acceptable, and 20% reported treatment only once per month would be acceptable • The most common barriers to treatment include: transportation (21.1%), hoping to feel better on their own (17%) work schedule (14%) and no money (10.4%) Study 2: • After viewing an information video, 13.7% responded that they would consider rTMS, 52.9% said they would not and 33.3% were undecided
Mayer[32] 2012, Australia	**Patient Selection**: Adolescents who had participated in a pilot study on rTMS for treatment resistant depression, and the parents of these individuals were eligible for inclusion in this study. **Inclusion Criteria:** Diagnosis of treatment resistant depression, adolescent, had prior treatment with rTMS OR parents of adolescent who met the above inclusion criteria **Exclusion Criteria:** Diagnosis of schizophrenia or bipolar disorder, history of epilepsy, psychosis or substance abuse **Patient Characteristics:** Twenty-one participants were included in this study; eight adolescents who had been treated with rTMS, and thirteen parents of those adolescents. The eight adolescents (2 males, 6 females) had a mean age of 20.4 (range 19-22). The parent cohort consisted of 8 females and 5 males (no mean age reported).	Self-administered questionnaire consisting of 48 (adolescents) or 51 (parents) items including: demographics, experience with rTMS, knowledge about the procedure, and attitudes towards rTMS	• rTMS recipients and their parents found rTMS largely acceptable in terms of adverse effects and treatment experience • 75% of the adolescents were unafraid of the procedure, six reported it was equally or less frightening than a dentist appointment • Five adolescents reported that rTMS did not improve their life significantly; one felt the treatment worsening their condition; two felt improvement • Six adolescents would recommend having rTMS to others who are treatment resistant; eight parents would recommend this treatment
Rosedale[33] 2009, United States	**Patient Selection**: Participants who had completed the OPT-TMS depression study in October 2008 were eligible for inclusion **Inclusion Criteria:** Not reported **Exclusion Criteria:** Not reported **Patient Characteristics:** Nine participants were included in this study. No other characteristics are reported.	Giorgi's phenomenology method was used; each participant was asked to describe the experience of undergoing rTMS for depression treatment and encouraged to provide as much detail as possible. Interviews were 1.5-2.5 hours in length.	• 4 preliminary themes identified by this study include: • A narrative of frustration and helplessness with medication treatment resistance • The sensory experience of rTMS • Mindfulness and enhanced awareness of the content of consciousness during treatment • The importance of connection with clinicians

Walter[34] 2001, Australia	**Patient Selection**: Patients who had received rTMS treatment at the Royal Boart Hospital between November 1996 and October 1999 were considered for inclusion. **Inclusion Criteria:** Had received antidepressant treatment, right-handed, no history of epilepsy or intracranial metal, treated with 10-15 sessions of rTMS provided 5 times per week **Exclusion Criteria:** None reported **Patient Characteristics:** Forty-eight participants (16 male, 32 female) with a mean age of 49 (range 23-79) were included.	Telephone survey consisting of 60 items including: demographics, experience with rTMS, knowledge of procedure, attitudes towards rTMS.	• Experience and opinions about TMS were generally very positive • 88% of participants responded that rTMS was less frightening than a dental appointment • 65% of participants reported that rTMS was helpful; one patient (2%) reported worsening and 29%reported no improvement • The vast majority rated TMS as more acceptable than having, or the prospect of having, ECT • 87% would have TMS again and would recommend it to others

ECT Electroconvulsive Therapy; **rTMS** Repetitive Transcranial Magnetic Stimulation

One study used phenomenology to explore the lived experience of patients with TRD[33]. In this study, in-depth open-ended interviews were conducted with nine patients who had been part of a rTMS randomized controlled trial (RCT) conducted in the U.S. The study article describes patients' experiences with the entire rTMS treatment process, including the important role played by clinicians who are administering the treatment[33]. The authors note that the narrative of frustration and helplessness with medication resistance is emerging as a main theme: "long histories of multiple medication trials, adverse reactions, intolerable side effects, and feeling like a failure were described"[33].

The other three studies used survey methods to explore the patient experience with[32;34], and/or their attitudes toward rTMS[31]. The purpose of the study by Walter et al. was to ascertain patient experience, knowledge and attitudes in relation to rTMS, and to make comparisons with other treatments rTMS recipients had been given, with a particular interest in ECT[34]. Approximately 2/3rd's of the 48 patients who participated in this study had prior experience with ECT[34]. A 60-item survey was developed, with several items adapted from an instrument developed for similar studies of ECT, and administered over the phone[34]. The various aspects of rTMS were generally considered 'not upsetting at all' by respondents[34]. However, the following were rated as 'very upsetting' by some patients: waiting for the treatment (n = 6, 12%), having a magnetic field applied (n = 1, 2%), developing a headache (n = 1, 2%), and the 'whole experience' of rTMS (n = 3, 6%)[34]. The vast majority of patients found rTMS to be an acceptable treatment, less aversive than the illness for which it was prescribed, and in many ways preferable to ECT[34]. The finding that rTMS was generally preferred to ECT is, perhaps, not surprising. Unlike ECT, rTMS is not administered under a general anaesthetic, does not produce a seizure and has not been subject to negative media portrayals. Note that this study was done more than a decade ago, and the kind of rTMS used is not specified.

The purpose of the study done by Kim et al. was to determine the acceptability of rTMS to pregnant women assessed as being depressed[31]. Depression was assessed as having a score of greater than or equal to 12 on the Edinburgh Depression Rating Scale (EPDS)[31]. This study found that virtually no women would consider rTMS as an acceptable treatment when it was just presented as one of a list of possible treatments[31]. When women are given more information about rTMS, however, its acceptability increased dramatically[31]. Improving knowledge about rTMS, then, improves acceptability. It was thought that another potential acceptability issue would be the time burden associated with receiving rTMS treatments, since most treatment protocols require treatment daily

for at least 20 sessions. In this study, an unexpectedly high proportion of subjects (50%) were agreeable to daily treatment for 4 weeks[31]. rTMS has a low burden of side effects but is time intensive. It was surprising to see how many women did not view this level of time commitment as a barrier. The most commonly reported barriers to rTMS treatment were difficulty arranging transportation for treatment, a belief that symptoms would improve without intervention, and difficulty accommodating work schedules[31]. This study concluded that for those women who do not respond to psychotherapy, which is currently recognized as the first line of treatment for depression during pregnancy, rTMS is a potential non-pharmacologic treatment[31].

The purpose of the study conducted by Mayer et al. was to describe the experience, knowledge, and attitudes regarding rTMS among young people (aged 19-22) who had been treated with rTMS as adolescents, as well as describe the views of their parents; and then compare these to opinions about pharmacotherapy (i.e., this group of adolescents had also been treated with fluoxetine for depression)[32]. Eight young people and 13 parents (8 mothers, 5 fathers) were recruited and participated in this study[32]. The questionnaires used were developed based on questionnaires that had previously been used to assess adolescent and parent views on ECT, and adults views on rTMS[32]. Most of the rTMS subjects and their parents did not experience the treatment as very frightening or upsetting, and most subjects and parents recalled more medication adverse effects than rTMS adverse effects[32]. In summary, this small study found that rTMS seems to be well tolerated by depressed adolescents and that the overall experience is not unpleasant for young people and parents[32]. These recipients and their parents, however, also did not perceive rTMS to be very helpful[32]. The study authors outline a number of reasons for the low estimate of benefit in the adolescent rTMS group, and note that the main limitation of this study – and particularly regarding the patient-assessed treatment effectiveness – is the small sample size[32].

4.1.4 Conclusions

Key themes emerged from these four studies. Patients and family members of adolescent patients were generally very positive about the treatment experience, reporting that the treatment is acceptable and well tolerated. Unlike ECT, rTMS is not administered under a general anaesthetic, does not produce a seizure and has not been subject to negative media portrayals. Patients and family members had mixed perspectives on the effectiveness of rTMS for TRD. For pregnant women who are depressed, improving knowledge about rTMS improves its acceptability. This is not surprising, as rTMS is a somewhat new treatment for depression and so many people do not know much or anything about it. Finally, the phenomenological study illustrated that

qualitative research that explores patient experience in more depth has the potential to increase our understanding of the whole treatment experience. This one published study described both how devastating TRD is for people living with it, and how important the therapeutic relationship is that develops between the patient and the clinician through the daily rTMS treatments.

5 Safety and Efficacy of Repetitive Transcranial Magnetic Stimulation

Summary of Efficacy and Safety Findings:

- *The clinical efficacy systematic review identified 70 relevant randomized controlled trials*
- *The included studies were of moderate quality, with most having a combination of unclear and low risks of bias, and few having high risks of bias*
- *rTMS is twice as likely to result in response and remission than sham*
- *The optimal rTMS protocol is unclear with no statistically significant differences in response and remission rates between high and low frequency, unilateral and bilateral, and high and low intensity rTMS*
- *The effectiveness of rTMS compared to ECT is unknown with conflicting findings, although not statistically significant, for response and remission*
- *rTMS did not increase minor adverse events (headaches, discomfort, nausea). Major adverse events were not assessed (suicide ideation, seizures).*

5.1 Research Objective

To determine the safety and effectiveness/efficacy of rTMS.

5.2 Methods

5.2.1 Literature Search

A systematic review was completed. MEDLINE, Cochrane CENTRAL Register of Controlled Trials, PubMED, EMBASE, PsycINFO, the Cochrane Database of Systematic Reviews and the HTA Health Technology Assessment Database were searched from inception until January 10th, 2014. Terms aimed at capturing the target diagnosis, such as "depression," "depressive disorder" and "bipolar disorder" were combined using the Boolean Operator "or." These terms were then combined, using the Boolean Operator "and" with terms describing the technology, such as "trancranial magnetic stimulation" and "rtms." Results were limited to humans and RCTs. No other limitations were used. Details of this search can be found in **Appendix C**.

5.2.2 Selection of Literature

All abstracts were screened in duplicate (LL and SC). Articles proceeded to full-text review if the study included only treatment resistant participants (as defined by the authors); adult participants (18 years and older); and reported on the efficacy of rTMS compared to sham, another method of rTMS, or another comparator (ECT, cognitive therapy, pharmaceuticals); the participants had a diagnosis of unipolar or bipolar depression; all

participants were naïve to rTMS treatment; and the study was a RCT (parallel-group or crossover designs were included). Abstracts were excluded if they did not meet the criteria above, if the study did not report original data or included animals, and/or data was only available as an abstract or poster. Abstracts selected for inclusion by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after abstract review proceeded to full-text review in duplicate (LL and SC). Studies were included if they met all inclusion criteria and failed to meet any of the criteria for exclusion presented in **Table 4**. Studies were included into one of six categories based on their comparator:

1. rTMS versus sham
2. rTMS versus another comparator (e.g. ECT, pharmaceuticals)
3. High frequency rTMS versus low frequency rTMS
4. Unilateral rTMS versus bilateral rTMS
5. High intensity rTMS versus low intensity rTMS
6. rTMS versus another type of rTMS protocol (e.g. left/right cortex, image guided rTMS, scheduling of sessions)

Trials with 3 arms were included in all appropriate categories. For example, a trial including a high frequency, low frequency and sham arm was included in both category 3 (high vs. low) and category 1 (rTMS vs. sham). The arm identified as "standard of care" was selected as the rTMS intervention arm for inclusion in category 1. Any discrepancy between reviewers was resolved through consensus. Full-text review was completed in duplicate. Published systematic reviews and meta-analysis on rTMS were hand-searched to ensure all relevant papers were captured in the literature search.

Table 4: Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
▪ Report TRD or report patients have had 2+ previous treatments ▪ Adult (≥ 18 years) population ▪ Report on one of the following: o Efficacy of rTMS in comparison to placebo, pharmacological therapy, cognitive therapy or ECT o Efficacy of one type/protocol of rTMS treatment in comparison to another type/protocol of rTMS treatment ▪ Bipolar or unipolar depression ▪ Report remission and/or response rates using the Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale or the Beck Depression Inventory ▪ Patients who have not been treated with rTMS prior to study ▪ RCT study design	▪ Not TRD or do not report whether patients have TRD ▪ Not rTMS ▪ Not unipolar or bipolar depression ▪ Non-original data ▪ Animal models ▪ Preclinical and biological studies ▪ Studies reported only in abstract or as poster presentations ▪ Not reporting on efficacy of rTMS ▪ Studies including patients who have not responded to rTMS in previous treatments ▪ Does not report outcomes using a depression rating scale

5.2.3 Data Extraction

For all studies, year of publication, country, patient selection, patient characteristics, definition of treatment resistance, description of technologies, protocols for control and treatment, outcomes measured, instruments used, definition of response, definition of remission and follow-up time were extracted using standardized data extraction forms. Response and remission outcomes were extracted from each study. Safety outcomes including headaches, nausea, discomfort, seizures, and suicide ideation were also extracted. Discrepancies between reviewers during data extraction were resolved through consensus.

5.2.4 Quality Assessment

During data extraction, each included study was assessed for quality using The Cochrane Risk of Bias Checklist[35]. Quality assessment was completed in duplicate with discrepancies being resolved through discussion. Using this checklist, each study was assessed for seven areas of bias (random assignment generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and any additional potential sources of bias)[35]. Each study is assigned "low, "high," or "unclear" risk of bias for each of these seven potential sources of bias[35].

5.2.5 Statistical Analysis

Five separate analyses were conducted, based on the comparator groupings established during data extraction (as outlined above). Response and remission rates were the primary outcomes considered in each of these five groupings. For each study, the number of participants who experienced remission and response were compared between the rTMS group and the comparator group. The definitions of response and remission, as defined by the papers' authors, were used in this analysis.

A random-effects model was used in all meta-analyses to assess the efficacy of rTMS in relation to other comparators. The random effects model assumes a normal distribution of effect size and different underlying effect for each study, allowing for between-study variation in the calculation. Meta-analyses were conducted using risk ratio (or relative risk) to express the efficacy of rTMS in relation to other comparators. Beggs Funnel plots were completed to assess the risk of publication bias.

All analyses were completed in STATA (STATA/IC 12.0).

5.3 Results of Technology Effects and Effectiveness

5.3.1 Regulatory Status

rTMS therapy was approved by Health Canada for clinical delivery in Canada in 2002 [22]. Currently, two companies (Magstim and Tonica Elektronik) have multiple machines licensed for use in Canada. Table 5 summarizes the rTMS machines reported in the published literature and their regulatory status in Canada.

Table 5: Summary of rTMS machines used in the Published Literature

Device	*List of Studies using Device*	*Approved for use in Canada?*
Magpro Stimulator (Magpro Compact, MagPro X100, Magpro R30) Produced by Tonica Elektronik A/S	Avery 2006[1], Avery 2007[2], Eche 2012[3], Fitzgerald 2006a[4], Blumberger 2012[5], Fitzgerald 2006b[6], Fitzgerald 2007[7], Fitzgerald 2008[8], Fitzgerald 2009a[9], Fitzgerald 2009b[9], Fitzgerald 2011[10], Fitzgerald 2012[11], Fitzgerald 2013[12], Galletly 2012[13], Garcia-Toro 2001[14], Garcia-Toro 2006[15], Holtzheimer 2004[16], Moller 2006[17], Peng 2012[18], Richieri 2012[19], Rosa 2006[20], Speer 2009[21], Zheng 2010[22]	Yes
Magstim Stimulator (MAGSTIM Rapid II, MAGSTIM Model 200	Baeken 2009[23], Baeken 2013[24], Bakim 2012[25], Bares 2009[26], Bortolomasi 2007[27], Boutros 2002[28], Bretlau 2008[29], Chen 2013[30], Fitzgerald 2003[31], GrunHaus 2000[32], Hernandez-Ribas 2013[33], Janicak 2002[34], Jorge	Yes

2, Neurosign Model 400) Produced by Magstim	2004[35], Jorge 2008[36], Levkovitz 2009[37], Loo 1999[38], Loo 2003[39], Loo 2007[40], Manes 2001[41], Mantovani 2013[42], Miniussi 2005[43], Moser 2002[44], Mosimann 2004[45], Padberg 1999[46], Padberg 2002[47], Paillere 2010[48], Pallanti 2010[49], Price 2010[50], Pridmore 2000a[51], Pridmore 2000b[52], Rossini 2005[53], Rossini 2010[54], Rybak 2005[55], Schrijvers 2012[56], Spampinato 2013[57], Su 2005[58], Triggs 2010[59], Turnier Shea 2006[60], Vanderhasselt 2009[61]	
Cadwell Stimulator	Berman 2000[62], Conca 2002[63], Pascual-leone 1996[64]	No
Neotonus Neopulse	Isenberg 2005[65]	No
Mag-lite Stimulator	Kauffmann 2004[66]	No
Neuro-MS (Neurosoft)	Keshtkar 2011[67]	No
Neuronetics Magnetic Stimulator	McDonald 2006[68], O'Reardon 2007[69], Solvason 2013[70], Zarkowski 2009[71]	No

5.3.2 Summary of Findings

Seventy papers were identified. Six categories based on comparator were developed: rTMS versus sham, rTMS versus ECT, high and low frequency rTMS, bilateral and unilateral rTMS, high and low intensity rTMS, and other rTMS protocols. No studies were found comparing rTMS with pharmaceuticals or cognitive therapy. Overviews of the findings in each category are represented in **Table 6**.

Table 6: Summary of Findings from Meta-analysis

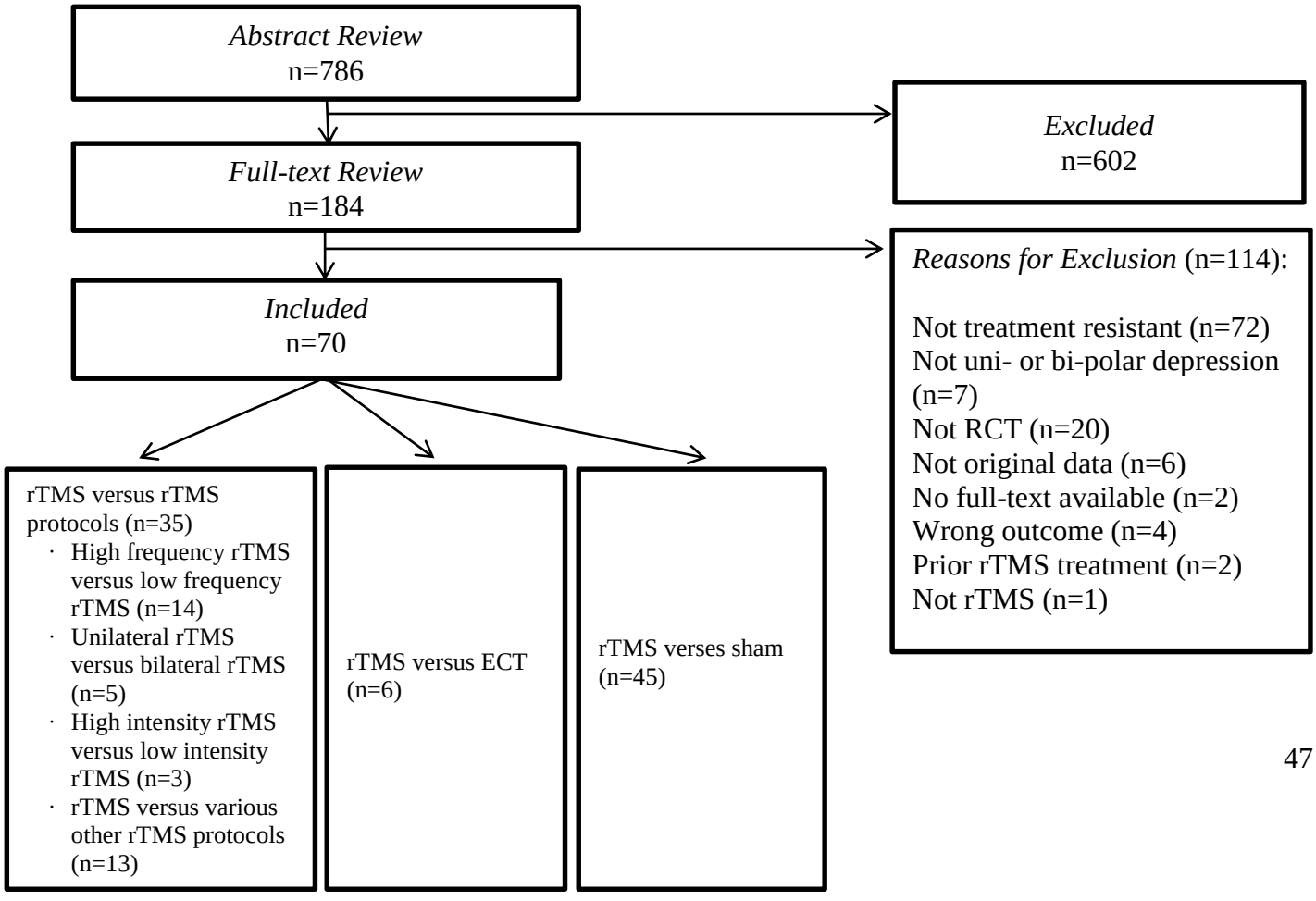
Comparator	Outcome Measure	Number of Pooled Studies (n)	Risk Ratio (95% Confidence Interval)	I^2 (%)	Figure(s)	Conclusion
rTMS versus Sham	Response	31	2.35 (1.70-3.25)	36.1	*Forest plot:* **Figure 3** *Funnel plot:* **Figure 4**	rTMS is an effective treatment. Patients undergoing rTMS are twice as likely to achieve either clinical response or remission than patients undergoing a sham procedure.
	Remission	18	2.24 (1.53-3.27)	1.1	*Forest plot:* **Figure 5** *Funnel plot:* **Figure 6**	
High frequency rTMS versus low frequency rTMS	Response	11	1.19 (0.97-1.46)	0.0	*Forest plot:* **Figure 7** *Funnel plot:* **Figure 8**	The optimal frequency of rTMS is unclear. There is trend towards high frequency rTMS being more effective to achieve both clinical response and remission than low frequency. However, both 95% confidence intervals cross 1.0 indicating that compared to low frequency, high frequency rTMS may be equivalent, more effective or less effective.
	Remission	6	1.29 (0.75-2.22)	8.1	*Forest plot:* **Figure 9** *Funnel plot:* **Figure 10**	
Unilateral rTMS versus bilateral rTMS	Response	5	1.15 (0.85-1.52)	45.8	*Forest plot:* **Figure 11**	The optimal location of treatment for rTMS is unclear. There is a trend towards bilateral rTMS being more effective to achieve both clinical response and remission than bilateral. However, both 95% confidence intervals cross 1.0 indicating that compared to bilateral, unilateral rTMS may be equivalent, more effective or less effective.
	Remission	3	1.18 (0.71-1.96)	53.6	*Forest plot:* **Figure 12**	
Low Intensity rTMS versus High Intensity rTMS	Response	3	1.15 (0.54-2.41)	57.3	*Forest plot:* **Figure 13**	The optimal intensity of rTMS is unclear. There is trend towards high intensity rTMS being more effective to achieve both clinical response and remission than low intensity. However, both 95% confidence intervals cross 1.0 indicating that compared to low intensity, high intensity rTMS may be equivalent, more effective or less effective.
	Remission	3	1.72 (0.89-3.33)	0.0	*Forest plot:* **Figure 14**	
rTMS versus other rTMS protocols	Narrative summary	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Experimentation to identify the optimal rTMS protocol is ongoing with research exploring the impact of image-guided, scheduling and combination therapy.
rTMS versus ECT	Response	3	1.09 (0.79-1.48)	0.0	*Forest plot:* **Figure 15**	The effectiveness of rTMS compared to ECT is unclear. There is trend towards rTMS being more effective to achieve clinical response but less effective to achieve remission. However, both 95% confidence intervals cross 1.0 indicating that compared to ECT, rTMS may be equivalent, more effective or less effective.
	Remission	3	0.97(0.65-1.45)	0.0	*Forest plot:* **Figure 16**	

5.3.3 Characteristics of Included Studies

A total of 786 citations were identified from the literature search. Of those, 602 were excluded during abstract review and 184 proceeded to full-text review. An additional 114 articles were excluded following full-text review, and 70 articles were included in the final analysis (see **Figure 2**). Five published systematic reviews and meta-analyses were hand-searched for articles not captured in the original search, and no additional papers were identified[36-40].

The final 70 papers were further allocated into six categories based on comparator: rTMS versus sham (n=45), rTMS versus ECT (n=6), high and low frequency rTMS (n=14), bilateral and unilateral rTMS (n=5), high and low intensity rTMS (n=3), and other rTMS protocols (n=13). Eighteen of the included studies had three comparator arms (two rTMS arms and a sham arm); these eighteen studies were included in both the rTMS versus rTMS and the rTMS versus sham categories. No studies were found comparing rTMS with pharmaceuticals or cognitive therapy.

Figure 2: Flow Chart of Studies Included in the Review of Repetitive Transcranial Magnetic Stimulation



5.3.4 Repetitive Transcranial Magnetic Stimulation Compared to Sham

5.3.4.1 Characteristics of Included Studies

Forty-five RCTs assessing rTMS compared to sham were included. Characteristics of each included study have been summarized in **Table 7**. One study was conducted in Canada[41], twenty-one studies in the United States[42-62], five in Australia[63-67], four in Spain[68-71], three in China[72-75], two in Germany[76]; two in Italy[77;78], and the remaining six were conducted in various other countries (Turkey[79]; Belgium[80]; Czech Republic[81]; Denmark[82]; France[83]; Iceland[84]). The studies were published between 1996[71] to 2013[54;60;70;72;80]. Fifteen studies used an intention-to-treat analysis[41;43;46;48;51;52;55;64;66;67;81;83;85-87], one reported using a per-protocol analysis[77], and the remaining did not report what type of analysis was conducted.

The number of participants included in each study varied between 6[42] and 301[58] participants, with a total of 1903 participants included in all forty-five studies combined. The inclusion and exclusion criteria varied greatly across studies. However, all participants were diagnosed with unipolar or bipolar disorder and all were treatment resistant. Treatment resistance was defined differently amongst the included studies; some reported a cut-off of at least one adequate trial of antidepressants as the definition of treatment resistance[44;46;48;53;54;58;66;67;70;81;82], while others reported patients had to have failed to respond to at least 3[55] in order to qualify as treatment resistant. However, the most common definition was failure to respond to two medications with 25 studies using this definition.

The protocol used for rTMS varied amongst the included studies. Frequency of rTMS used varied from 1[50;54;64;69;81] to 20[45;53;56;57;59;60;68;72;74;77;79;80;85] hertz (Hz), and motor threshold varied from 80%[42;45;53;56;85] to 120%[51;65;87;88]. Number of rTMS sessions provided to each participant in the active arms varied from 5 to 30, over a period of 5 days to 6 weeks.

The protocol used for sham procedure was similar in all studies, with most using an rTMS machine turned on, but with the machine at a 45 degree angle from the patient. Using this method, the patient would feel the machine vibrations but would not experience a treatment effect.

Table 7: Characteristics of Studies Assessing the Efficacy of rTMS versus Sham

Author, Year of Publication, Country	*Patient Selection*	*Comparators*	*Outcomes*
Avery[42] 1999, United States	**Patient Selection:** Patients were recruited through authors practice and other practitioners and were randomized to sham or active rTMS **Inclusion Criteria:** DSM-IV major depression or bipolar disorder (depressed phase), treatment resistant, right handed, 20 or more on Hamilton Depression Rating Scale **Exclusion Criteria: Patient Characteristics:** metal in body, cardiac pacemaker, implanted electronic device, history of head injury associated with loss of consciousness, brain surgery, epilepsy, labile or hypertensive blood pressure, other major psychiatric or medical illnesses, suicidal intent or plans **Patient Characteristics:** Four participants (all female) received active rTMS. Two participants (1 female, 1 male) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to two or more antidepressants	**Type of Control** Sham rTMS with stable dose of current ineffective medication for at least 6 weeks prior to start of trial, or medication free **Type of Comparator** active 10 Hz rTMS to left prefrontal cortex at 80% motor threshold for 10 sessions during 16 days	**Outcomes measured:** Hamilton Depression Rating Scale, Beck Depression Inventory, Clinical Global Impression, Galveston Orientation and Amnesia Test, Rey Auditory Verbal Learning Test, Controlled Oral Word Association Test, Trail Making A and B, Stroop Color Word Test, WAIS-R Digit Span, Digit Symbol subtest **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, after 5th session, after 10th session, 1 week after completion of treatment, 2 weeks after completion of treatment **Type of Analysis:** Not reported
Avery[43] 2006, United States	**Patient Selection:** Patients were recruited through physician referral and advertisement between Jan. 2001- Feb. 2004, and were randomized by computer program. **Inclusion Criteria:** Age 21-65, current major depressive disorder as diagnosed by DSM-IV, treatment resistant, score of 17 or more on HAM-D **Exclusion Criteria:** Prior rTMS, bipolar disorder, failure of nine or more ECT treatments, substance abuse or addiction in past 2 years, antisocial or borderline personality disorder, psychosis, seizure disorder, closed head injury with loss of consciousness, brain surgery, major psychiatric or medical comorbidity **Patient Characteristics:** Thirty-five participants with a mean age of 44.3(10.3), 21 females and 14 males were randomized to the active group. Thirty-th68ree participants with a mean age of 44.2(9.7), 16 females and 17 males were randomized to the control group **Definition of Treatment Resistance:** Failure to respond to two or more antidepressants	**Type of Control** Sham rTMS with stable dose of current medication for 4 months or medication-free for 2 weeks **Type of Comparator** active 10 Hz rTMS to left DLPC at 110% motor threshold for 15 sessions over 4 weeks (2,400 total pulses)	**Outcomes measured:** Hamilton Depression Rating Scale, Beck Depression Inventory, Re y Auditory Verbal Leaning Test, Digit Symbol Test and Digit Span, Mini-Mental State Examination, Stroop Test, Controlled Word Association Test, Galveston Orientation and Amnesia Test, Systematic Assessment for Treatment Emergent Effects (SAFTEE) **Follow-up time:** 5 weeks **Outcome ascertainment:** Baseline, visit 5, 10, 15 and 1 week after last session **Type of Analysis:** Intention-to-treat
Baeken[80] 2013, Belgium	**Patient Selection:** Participants were selects as part of a larger project looking at the influence of HF-rTMS on neurocognitive markers. All participants were included after screening by the Mini-international Neuropsychiatric Interview. Participants were randomized to receive active rTMS, followed by sham rTMS. **Inclusion Criteria:** right handed, unipolar depression diagnosis, treatment resistant **Exclusion Criteria:** history of epilepsy, neurosurgical interventions, pacemaker, metal or magnetic objects in the brain, Alcohol dependence, suicide attempts in prior 6 month **Patient Characteristics:** Twenty participants (13 females, 8 males), mean age 49.33(12.50) were included and received both sham and active rTMS in cross-over design. **Definition of Treatment Resistance: M**inimum of two unsuccessful treatment trials with serotonin reuptake inhibitors/ noradrenaline and/or serotonin reuptake inhibitors and one failed clinical trial with a tricyclic antidepressant	**Type of Control** sham rTMS on no medication **Type of Comparator** 20 HZ rTMS stimulation to the left dorsolateral prefrontal cortex at 110% motor threshold for 20 sessions during 4 days. Participants were on no mediation; total of 31,200 stimulations over 4 days	**Outcomes measured:** Hamilton Depression Rating Scale **Follow-up time:** Two weeks **Outcome ascertainment:** Baseline, after 1 week, and after 2 weeks **Type of Analysis:** Not reported

Bakim[79] 2012, Turkey	**Patient Selection:** Patient volunteers were recruited at 1 psychiatric outpatient clinic (no recruitment dates specified) and were randomized by computer program. **Inclusion Criteria:** Age 18-65, a diagnosis of unipolar major depression, recurrent or single episode and without psychotic features, treatment resistant depression, score of 18 or more on HAM-D or 20 on the MADRS, right-handedness **Exclusion Criteria:** comorbidity of any other Axis I disorder, including alcohol and substance use disorders, current or past history of epilepsy, head trauma, encephalitis, meningitis, or any other cerebrovascular disease, pregnancy, any pace-maker or medical pumps replaced in the body or a metal implant in the skull, any use of ECT, antipsychotics or anticonvulsants which may interfere with the excitability of cortical neurons and change the motor threshold, inability to read and understand the Turkish language. **Patient Characteristics:** Eleven participants with a mean age of 43.1 (8.2), 10 females and 1 male were randomized to high intensity rTMS. Twelve participants with a mean age of 44.41(10.22), 11 females and 1 male, were randomized to sham rTMS. **Definition of Treatment Resistance:** No response to adequate courses (at least 6 weeks) of at least two different classes of antidepressants used at optimal doses	**Type of Control** sham rTMS **Type of Comparator** 20 Hz rTMS to left DLPFC at 110% motor threshold for 20 trains of 40 pulses (24000 total treatment) once per day for 6 weeks	**Outcomes measured:** Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline and every week **Type of Analysis:** Not reported
Bares[81] 2009, Czech Republic	**Patient Selection:** Patients were recruited from the Prague Psychiatric Centre between June 2005 and July 2008 due to lack of treatment response and were randomized using a permuted block design (Various outpatient clinics and psychiatric hospitals) **Inclusion Criteria:** 18-65 years old, Score of 20 or more on the Montgomery-Asberg Depression Rating Scale, and were determined to be treatment resistant **Exclusion Criteria:** Suicide risk, current psychiatric comorbidity on axis I, personality disorder, serious unstable medical illness, drug or alcohol abuse, risk of seizure, pregnancy or women who were nursing, previous treatment of fluoxetine, resistant to venlafaxine **Patient Characteristics:** Twenty-seven participants, mean age of 45.4(11.7) and 22 females, 5 males were randomized to the active rTMS group. Thirty-one participants with a mean age of 44.2(11.6), 24 females and 7 males, were randomized to receive sham rTMS and venlafaxine ER **Definition of Treatment Resistance:** Failure to respond to at least one antidepressant treatment	**Type of Control** sham rTMS with 75mg of venalafaxine ER on days 1-5, increasing to 375mg by the end of the study **Type of Comparator** active 1 Hz rTMS to the right dorsolateral prefrontal cortex at 100% motor threshold for 20 sessions over 4 weeks (600 pulses per session)	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory short form, Clinical Global Impression **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, week 1, 2,3 and 4 **Type of Analysis:** Intention-to-treat
Berman[85] 2000, United States	**Patient Selection:** Patients were selected who met the inclusion criteria, and were randomized to receive sham or active rTMS **Inclusion Criteria:** Age 18-70, met DSM-IV criteria for major depressive episode, treatment resistant, no diagnosis of substance or alcohol abuse, no history of neurologic illness **Exclusion Criteria:** Pregnancy, EEG abnormality suggestive of epileptic predisposition, significant unstable medical illness **Patient Characteristics:** Twenty participants with a mean age of 44.3, 6 females and 14 males were included, Three sham discontinued due to lack of response **Definition of Treatment Resistance:** Failed at least one pharmacologic trial during current or previous episode	**Type of Control** sham rTMS with no antidepressants, neuroleptics or benzodiazepines for one week prior to starting sham procedure **Type of Comparator** active 20 Hz rTMS to the left dorsolateral prefrontal cortex, delivered at 80% motor threshold for 10 consecutive weekdays	**Outcomes measured:** Hamilton Depression Rating Scale, side effects checklist, Beck Depression Inventory, Hamilton Anxiety Scale **Follow-up time:** Two weeks **Outcome ascertainment:** Baseline, each day for 10 consecutive weekdays **Type of Analysis:** Intention-to-treat
Blumberger[41] 2012, Canada	**Patient Selection:** Patient volunteers recruited from 3 outpatient clinics from Jan 2006 to Jan 2009 and were randomized using a computer-generated list. **Inclusion Criteria:** Age 18-85, DSM-IV diagnosis of MDD without psychotic features based on the Structured Clinical Interview for DSM-IV, treatment resistant depression, score of greater than 21on HAM-D, receiving stable doses of psychotropic medications for at least four weeks prior to randomization, capable to consent as assessed based on their ability to provide a spontaneous narrative description of the key elements of the study using the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR), currently an outpatient. **Exclusion Criteria:** DSM-IV substance dependence in the last 6 months (excluding nicotine) or DSM-IV substance abuse in the last month, mMet DSM-IV criteria for borderline personality disorder or antisocial personality disorder based on the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II), Bipolar I, II or NOS, had	**Type of Control** sham rTMS with coil angled at 90 degrees off the scalp **Type of Comparator** 10 Hz rTMS to HFL 100% motor threshold for 29 trains of 50 pulses (1450 total treatment) 5 days per week for 3 weeks	**Outcomes measured:** Hamilton Depression Rating Scale, Repeatable Battery for the assessment of Neuropsychological Status, Hopkins Verbal Learning Test (Revised), Brief Visual Memory Test (Revised), Grooved Peg Board test **Follow-up time:** 6 weeks **Outcome ascertainment:** baseline and every 5 treatments **Type of Analysis:** Modified IIT

	a significant unstable medical or neurologic illness or a history of seizures, acutely suicidal, pregnant, metal implants in the cranium, had a known diagnosis of dementia or a current MMSE score less than 26, had received benzodiazepines (dose equivalent > lorazepam 2 mg/day), monoamine oxidase inhibitors, or buproprion during the previous four weeks, received prior treatment with rTMS for any indication **Patient Characteristics:** Twenty-six patients with a mean age of 58.0 (12.5), 14 females, 12 males were randomized to unilateral rTMS. Twenty patients with a mean age of 45.8 (13.4), 14 females, 6 males were randomized to sham rTMS. **Definition of Treatment Resistance:** Failed to achieve a clinical response, or did not tolerate, at least two separate trials of antidepressants from different classes at sufficient dose for at least 6 weeks according to Stage II criteria outline by Thase and Rush		
Bortolomasi[77] 2007, Italy	**Patient Selection:** Patients who met the inclusion criteria were selected and randomized to receive sham or active rTMS **Inclusion Criteria:** Right handed, no history of brain trauma or seizure, normal neurological examination, treatment resistant, DSM-IV criteria for major depression **Exclusion Criteria:** Those with pacemakers, mobile metal implants, or implanted medical pumps **Patient Characteristics:** Twelve participants, ranging from 45-56 years old (7 females and 5 males) were randomized to receive active rTMS. Seven participants, four females and three males, ranging from 44-53 years old were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Not reported	**Type of Control** sham rTMS with unchanged medication (including tricyclic or serotonin reuptake inhibitors) **Type of Comparator** active 20 Hz rTMS, at 90% motor threshold (800 stimuli per day) targeting the left prefrontal area was given for five sessions per week over 4 weeks. Medication was unchanged during treatment (including tricyclic or serotonin reuptake inhibitors).	**Outcomes measured:** Hamilton Depression Rating Scale, Beck Depression Inventory **Follow-up time:**12 weeks **Outcome ascertainment:** Baseline, 1, 4, and 12 weeks **Type of Analysis:** Per protocol
Boutros[45] 2002, United States	**Patient Selection:** Outpatients meeting the inclusion criteria were randomized using a computer generated sequence **Inclusion Criteria:** Diagnosis of major depression, Treatment resistance, score of at least 20 on Ham-D scale **Exclusion Criteria:** Suicidal ideations, prominent psychotic symptoms, history of neurological disorder, history of drug abuse within the past 3 months **Patient Characteristics:** Twelve participants, with a mean age of 49.5 (8) were randomized to receive active rTMS. Nine participants with a mean age of 52(7) were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failed two prior medication trials judged to be of adequate dose and duration, or unwilling to try medication	**Type of Control** sham rTMS with unchanged medication for 2 weeks prior to rTMS and during treatment **Type of Comparator** active 20 Hz rTMS to the left prefrontal cortex for 10 consecutive weekdays (800 stimuli per session) at 80% motor threshold	**Outcomes measured:** Hamilton Depression Rating Scale **Follow-up time:** Five months **Outcome ascertainment:** Baseline and days 3,5,6,8 and 10 **Type of Analysis:** Not reported
Bretlau[82] 2008, Denmark	**Patient Selection:** Participants were recruited between April 2003 and December 2005, by general practitioners. **Inclusion Criteria:** Age 18-75, meet DSM-IV criteria for current major depressive disorder, treatment resistant **Exclusion Criteria:** organic brain disorder, substance abuse, severe anxiety disorder, personality disorder, history of epilepsy, metal implants in head or neck, pacemaker, suicidal ideation (score of more than 2 on the suicide item of Ham-D), those receiving antipsychotics, current episode has lasted longer than 24 months, risk factors deterring escitalopram treatment, pregnancy **Patient Characteristics:** Twenty-two participants, with a mean age of 53.1 (10.1), 7 males and 15 females, were randomized to receive active rTMS. Twenty-three participants, with a mean age of 57.8(10.0), 10 males and 13 females, were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failed to respond to at least one adequate antidepressant treatment during current episode	**Type of Control** sham rTMS combined with 20mg escitalopram/day, but no other medication. **Type of Comparator** active 8 Hz rTMS to the left dorsolateral prefrontal cortex delivered at 90% motor threshold for 15 consecutive workdays (3 weeks) for a total of 19,200 pulses. Active rTMS was combined with 20mg escitalopram/day.	**Outcomes measured:** Hamilton Depression Rating Scale, Bech-Rafaelsen Melancholia Scale, UKU Scale, Major Depression Inventory **Follow-up time:**12 weeks **Outcome ascertainment:** Baseline, and 2,3,5,8 and 12 weeks **Type of Analysis:** Not reported
Chen[72] 2013, China	**Patient Selection:** Patients were recruited between January 1, 2008 and October 31, 2008 from one hospital in Taiwan, and randomized. **Inclusion Criteria:** Treatment resistant depression, score of greater than 18 on Ham-D, able to be in hospital during treatment, diagnosis of major depressive disorder by DSM-IV criteria **Exclusion Criteria:** High risk of suicide, head injury, epilepsy, implanted pacemaker **Patient Characteristics:** Ten participants, with an average age of 44.1 (4.4), 3 males and 7 females, were randomized to receive active rTMS. Ten participants, with an average age of 47.3(3.5), 6 males and 4 females, were randomized to receive sham rTMS.	**Type of Control** sham rTMS remaining on consistent antidepressant therapy **Type of Comparator** active 20Hz rTMS to the left dorsolateral prefrontal cortex delivered at 90% motor threshold for 10 sessions completed during 4 weeks	**Outcomes measured:** Beck Depression Inventory II, 17-item Hamilton Depression Rating Scale, Brief Psychotic Rating Scale, Young Mania Rating Scale **Follow-up time:** One month after completion of treatment **Outcome ascertainment:** Baseline, after 5th treatment, after 10th treatment, and one month after completing treatment.

	Definition of Treatment Resistance: No response to two different antidepressants over a period of 6 weeks each		**Type of Analysis:** Not reported
Fitzgerald[63] 2003, Australia	**Patient Selection:** Patients were recruited from 2 outpatient clinics and psychiatrists between Oct 2000 and Sept 2002 and were randomized via sealed envelopes. **Inclusion Criteria:** Not reported **Exclusion Criteria:** Significant medical illness, neurologic disorders or other Axis I psychiatric disorders **Patient Characteristics:** Twenty patients with a mean age of 49.15 (14.243), 11 females and 9 males were randomized to sham rTMS. Twenty patients with a mean age of 42.2 (9.8), 8 females and 12 males were randomized to high frequency left sided rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 2 courses of antidepressants medications for at least 6 weeks	**Type of Control** sham rTMS **Type of Comparator** 10 Hz rTMS to HFL 100% motor threshold for 20 trains (1000 stimuli per treatment) 5 days per week for 2 weeks	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory, Brief Psychiatric Rating Scale, CORE rating of psychomotor disturbance, Clinical Global Impression, Personal Semantic Memory Schedule, Autobiographical Wechsler Adult Intelligence Scale, Tower of London, Controlled Oral Word Association Test **Follow-up time:** 4 weeks **Outcome ascertainment:** baseline, 2 weeks, 4 weeks **Type of Analysis:** Not reported
Fitzgerald[64] 2006, Australia	**Patient Selection:** Patients were recruited from an outpatient department of a regional mental health department, or by referral by psychiatrist, between January 2003 and September 2004, and randomized to sham or active rTMS using a single random-number sequence **Inclusion Criteria:** Diagnosis of major depressive episode or bipolar I disorder based, treatment resistant, >20 on MADRS **Exclusion Criteria:** Significant medial illness, neurological disorder, another axis I psychiatric disorder **Patient Characteristics:** Twenty-five participants, mean age 46.8(10.7), 10 males and 15 females were randomized to receive active rTMS. Twenty-five participants, mean age 43.7(10.2), 9 males and 16 females were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least two trials of antidepressant medication for at least 6 weeks using a standard effective dose	**Type of Control** sham rTMS with no change in medication 4 weeks prior to or during the trial **Type of Comparator** active 1 Hz rTMS stimulation to the right dorsolateral prefrontal cortex delivered at 110% motor threshold followed by 10 Hz rTMS stimulation to the left dorsolateral prefrontal cortex delivered at 100% motor threshold. Participants had no change in medication 4 weeks prior to or during the trial	**Outcomes measured:** MADRS, Hamilton Depression Rating Scale, Beck Depression Inventory, Brief Psychiatric Rating Scale, CORE Rating of Psychomotor Disturbances, Global Assessment of Functioning Scale, Clinical Global Impression **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline, week 2,3,4,5, and 6 **Type of Analysis:** Intention-to-treat
Fitzgerald[65] 2012, Australia	**Patient Selection:** Patients were recruited from Jan 2008-Nov 2010 and were randomized (method not specified). **Inclusion Criteria:** Hamilton Depression Rating Scale score > 15 **Exclusion Criteria: bipolar disorder,** significant currently active medical illness, current neurological disease, contraindication to rTMS **Patient Characteristics:** Twenty-four patients with a mean age of 43.4 (12.7.1),15 females and 9 males were randomized to unilateral left high frequency rTMS. Seventeen patients with a mean age of 44.9(15.7), 8 females and 12 males were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 2 courses of antidepressants medications for at least 6 weeks in the current episode	**Type of Control** sham rTMS **Type of Comparator:** 10 Hz 120% motor threshold for 30 trains for 3 weeks	**Outcomes measured:** Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, Beck Depression Inventory, CORE rating of psychomotor disturbance, State-Trait Anxiety Inventory, Depressive Personality Disorders Inventory, Wechsler Test of Adult Reading, Rey Auditory Verbal Learning Test, Brief Visual Spatial Memory Test, Digit Span, Trail Making Test A & B, Stroop and COWAT phonemic Fluency **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline, 3 weeks, 6 weeks **Type of Analysis:** Not reported

Garcia-Toro[89] 2001, Spain	**Patient Selection:** Not reported **Inclusion Criteria:** Age 18 or older, DSM-IV diagnosis of unipolar major depression, treatment resistant, right-handed **Exclusion Criteria:** History of seizures or neurosurgery, serious or uncontrolled medial illness, pacemaker or hearing aid, pregnancy, women of childbearing potential lacking effective contraceptive, high suicidal risk **Patient Characteristics:** Seventeen participants (10 males, 7 females) with a mean age of 51.5(15.9) received active rTMS. Eighteen participants (10 males, 8 females) with a mean age of 50(11) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least two antidepressant medications at the maximum dose tolerated for a least 6 weeks during the current episode	**Type of Control** sham rTMS with patients taking stable doses of antidepressants for the six weeks prior to trial **Type of Comparator** active 20 Hz rTMS stimulation to the left Dorsolateral Prefrontal Cortex, delivered at 90% motor threshold for ten consecutive workdays. Stable dose of antidepressants for six weeks prior to trial.	**Outcomes measured:** Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale, Clinical Global Impression, Beck Depression Inventory **Follow-up time:** Four weeks **Outcome ascertainment:** Baseline, week 1, 2 and 4 **Type of Analysis:** Not reported
Garcia-Toro[69] 2006, Spain	**Patient Selection:** Not reported. Randomization occurred using sealed envelopes. **Inclusion Criteria:** Age > 18, unipolar major depression **Exclusion Criteria:** high suicidal risk **Patient Characteristics:** Ten patients with a mean age of 48.5 (13.3), 4 females and 6 males received rTMS. Ten patients with a mean age of 47.20(11.8), 7 females and 3 males received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 2 trials of antidepressants medications	**Type of Control** sham rTMS **Type of Comparator** Alternating 1 Hz at 110% motor threshold for 30 trains with 20 Hz at 110% motor threshold for 30 trains	**Outcomes measured:** Hamilton Depression Rating Scale, Clinical Global Impression **Follow-up time:** 10 sessions **Outcome ascertainment:** Baseline, 1 week, 2 weeks, 4 weeks **Type of Analysis:** Not reported
George[46] 2010, United States	**Patient Selection:** Patients were recruited between October 15, 2004 and March 31, 2009 using advertisement and referral. **Inclusion Criteria:** age 18-70, free of anti-depressant medication, DSM-IV diagnosis of major depressive disorder, current episode lasting less than 5 years, score of 20 or more on Ham-D, stable during 2 weeks free of medication, treatment resistance **Exclusion Criteria:** Other axis I disorders, fail to respond to electroconvulsive therapy, pervious treatment with rTMS or vagus nerve stimulation, family history of seizure disorder, neurologic disorder, ferromagnetic material in body or near head, pregnancy, taking medication which lowers seizure threshold, positive urine test for cocaine, marijuana, PCP or opiates **Patient Characteristics:** Ninety-two participants (34 male, 58 female) with a mean age of 47.7(10.6) received active rTMS. Ninety-eight participants (48 male, 50 female) with a mean age of 46.5(12.3) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to 1-4 antidepressants, or intolerant to 3 or more.	**Type of Control** sham rTMS with no medication **Type of Comparator** active 10 Hz rTMS stimulation to the left prefrontal cortex delivered using 110-120% motor threshold over three weeks for 15 total sessions, with no medication (3000 pulses per session)	**Outcomes measured:** Ham-D, Montgomery-Asperg Depression Rating Scale, Clinical Global Impression Severity of Illness Scale, Inventory of Depressive Symptoms **Follow-up time:** Three weeks **Outcome ascertainment:** Baseline, 3 weeks **Type of Analysis:** Intention-to-treat
Hernandez-Ribas[70] 2013, Spain	**Patient Selection:** Participants were recruited from the Mood Disorders Unit of the Bellvitge University Hospital. **Inclusion Criteria:** Right handed, non-psychotic major depressive or bipolar disorder, treatment resistant, stable dose of antidepressants during treatment and 6 weeks prior, DSM-IVcriteria for major depressive episode **Exclusion Criteria:** history of other axis I diagnosis, history of neurological condition, serious medical condition, abnormal MRI, presence of any factor preventing MRI acquisition **Patient Characteristics:** Ten participants (8 females and 2 males), mean age 42.6(5.56) were randomized to receive active rTMS. Eleven participants (8 females, 2 males), mean age 46.31(7.34) were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least one trial of adequate antidepressant	**Type of Control** sham rTMS with participants on stable dose of medications for at least 6 weeks prior to and during trial **Type of Comparator** 15 Hz rTMS stimulation to the left dorsolateral prefrontal cortex delivered using 100% motor threshold for 15 sessions over 3 weeks. Participants on stable dose of medication for at least 6 weeks prior to and during trial.	**Outcomes measured:** Hamilton Rating Scale **Follow-up time:** three weeks **Outcome ascertainment:** Baseline, week 1, 2 and 3 **Type of Analysis:** Not reported

Holtzheimer[86] 2004, United States	**Patient Selection:** Participants were recruited by physician referral, referral from centers doing ECT, and media advertisements between January 1998 and December 1999 **Inclusion Criteria:** Age 21-65, right handed, meet DSM-IV criteria for major depressive episode due to major depressive disorder, no major psychiatric or medical comorbidity, treatment resistant, score of at least 18 on Ham-D scale, not on medication **Exclusion Criteria:** History of bipolar disorder, failure to respond to electroconvulsive therapy, history of substance abuse, psychosis, pregnancy **Patient Characteristics:** Seven participants (4 females, 3males), mean age 40.4(8.5) received active rTMS. Eight participants (3 females, 5 males), mean age 45.4(4.9) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least two adequate trials of antidepressants	**Type of Control** sham rTMS on no medication **Type of Comparator** 10 Hz rTMS stimulations to the left dorsolateral prefrontal cortex delivered using 110% motor threshold for 10 sessions over two weeks (1600 pulses per day)	**Outcomes measured:** Beck Depression Inventory, Hamilton Depression Rating Scale **Follow-up time:** Three weeks **Outcome ascertainment:** Baseline, week 1, 2 and 1 week after final session **Type of Analysis:** Intention-to-treat
Jorge[49] 2004, United States	**Patient Selection:** Participants were recruited, at the University of Iowa Adult Psychiatry Outpatient Clinic, the University of Iowa Outpatient Cardiology Clinic and through newspaper advertisement **Inclusion Criteria:** Diagnosis of hemispheric, brainstem or cerebellar stroke, DSM-IV diagnosis of depression due to stroke, treatment resistant **Exclusion Criteria:** severe systemic disease, ongoing neoplasia, neurodegenerative disorder, clinical evidence of dementia, aphasic patients with language comprehension deficits, suicidal risk, prominent psychotic features, bipolar course, substance abuse during past 12 months, history of seizure, major head trauma, idiopathic epilepsy, metal in head or neck, cardiac pacemaker, implanted defibrillator, intracardiac lines, cortical lesions of the left frontal cortex **Patient Characteristics:** Ten participants (4 females, 6 males), mean age 63.1(8.1) received active rTMS. Ten participants (5 females, 5 males), mean age 66.5(12.2) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least two adequate trials of antidepressants	**Type of Control** sham rTMS with no medication **Type of Comparator** 10 Hz rTMS stimulation to the left prefrontal cortex delivered using 110% motor threshold for 10 sessions over three weeks with no medication	**Outcomes measured:** Hamilton Depression Rating Scale, premorbid intelligence quotients, Stroop Test, Trail Making Test A and B, Controlled Oral Word Association Test, Rey Auditory Verbal Learning Test, Benton Visual Retention Test, Boston Naming Test, Token Test, Sentence Repetition Subtest of the Multilingual Aphasia Examination, Wechsler Adult Intelligence Scale-III, Line Bisection Test, Mini Mental State Examination **Follow-up time:** Three weeks **Outcome ascertainment:** Baseline, 3 weeks **Type of Analysis:** Not reported
Jorge[48] 2008, United States	**Patient Selection:** Participants were recruited from the Department of Psychiatry at the University of Iowa hospitals, the Department of Psychiatry at the Iowa City Veterans Affairs Medical Center, and through advertising **Inclusion Criteria:** Age 50 or older, history of subcortical stroke, at least three cardiovascular risk factors (arterial hypertension, diabetes mellitus, obesity, hyperlipidemia, smoking), major depression as diagnosed by DSM-IV criteria, treatment resistance **Exclusion Criteria:** Severe heart or respiratory failure, renal or hepatic failure, occurrence of ongoing neoplastic process, neurodegenerative disorder, clinical evidence of dementia, suicide risk, prominent psychotic features, substance abuse within the prior two years, prior induced seizures, major head trauma, history of epilepsy, metal in head or neck, cardiac pacemaker, implanted defibrillator, medication pump **Patient Characteristics:** Fifteen participants (6 females, 9 males), mean age 62.9(7.2) received active rTMS. Fifteen participants (8 females, 7 males), mean age 66.1(11) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least one adequate trial of antidepressant	**Type of Control** sham rTMS **Type of Comparator** 10 Hz rTMS stimulation to the left dorsolateral prefrontal delivered at 110% motor threshold for 10 sessions over a 10 day period	**Outcomes measured:** Hamilton Depression Rating Scale, Rey Auditory Verbal Learning Test, Stroop Colour and Word Test, Trail Making Tests A and B, Controlled Oral Word Association Test, Functional Independence Measure, Mini Mental State Examination **Follow-up time:** 3 weeks **Outcome ascertainment:** Baseline, week 2, week 3 **Type of Analysis:** Intention-to-treat
Kauffmann[50] 2004, United States	**Patient Selection:** Unknown, randomized **Inclusion Criteria:** Over 18 years old, met DSM-IV criteria for major depression, treatment resistant **Exclusion Criteria:** Pre-existing neurological and/or cardiac diseases **Patient Selection:** Twelve patents with mean age of 51.7 (17.2), 11 females and 1 male, randomly assigned to receive active or sham rTMS, 7 in active group and 5 in sham group **Definition of Treatment Resistance:** Failure to respond to at least two antidepressants given for 8 weeks at adequate dosages	**Type of Control** Sham rTMS (same as comparator but 45 degree angle from the skull) with previous medication regimen **Type of Comparator** tangential to the skull, 1Hz, 0.1ms pulse duration, field intensity 10% above motor threshold, 10 treatments over 2 weeks. Participants could continue on previous medication regimen during rTMS treatment.	**Outcomes measured:** Hamilton Depression Rating Scale, SCL-90 **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, 1 week and after last session (2 weeks) **Type of Analysis:** Not Reported

Lisanby[51] 2009, United States	**Patient Selection:** Patients were recruited from twenty-three sites in the United States, Australia, and Canada, between January 2004 and August 2005, and were randomized **Inclusion Criteria:** DSM-IV diagnostic criteria for unipolar, nonpsychotic major depressive disorder, treatment resistant depression, medication free outpatient, age 18-70, Clinical Global Impression score at least 4, HAMD17 score at least 20 **Exclusion Criteria:** Risk factors for seizures **Patient Selection:** 164 participants who were treatment resistant were randomized to receive active rTMS. Sixty-seven participants (42 females), mean age 47(11.3) were randomized to receive active rTMS. Seventy participants (32 females), mean age 45.3(10.6) were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failure to respond to more than 1 adequate antidepressant trial	**Type of Control** Sham rTMS with medication free **Type of Comparator** 10 HZ rTMS to the left dorsolateral prefrontal cortex using 120% motor threshold, 4s in duration with 26s interval (40 pulses for each pulse train), 75 pulse trains, 3000 pulses	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, Hamilton Depression Rating Scale, ATHF, IDS-SR, Clinical Global Impression **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline, week 2, 4, 6, participants unblinded at 4 weeks **Type of Analysis:** Intention-to-treat
Loo[52] 1999, United States	**Patient Selection:** Unknown **Inclusion Criteria:** DSM-IV major depressive episode, treatment resistant depression, ≥25 on the Montgomery-Asberg Depression Rating Scale **Exclusion Criteria:** major physical or neurological abnormalities, treated with ECT during this depressive episode **Patient Selection:** 18 patients (9 male, 9 female), mean age real rTMS 45.7 (14.7) and for sham age 50.9(14.7). Nine participants, mean age 45.7(14.7) received active rTMS. Nine participants, mean age 50.9(14.7) were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Not reported	**Type of Control** Sham with or without continued antidepressants **Type of Comparator** 10Hz rTMS delivered at 110% motor threshold, 30 train of 5 seconds, 30 seconds apart; for 10 sessions over 2 weeks	**Outcomes measured:** Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, CPRE scale, self-rated Beck Depression Inventory, AUSSI scale, Mini-Mental State examination, digit span, simple and complex reaction time, Luria hand sequences, visual paired associates learning, verbal fluency, Tower of London, Rey Auditory Verbal Learning Test, Autobiographical Memory interview **Follow-up time:** 2 weeks (4 weeks of real rTMS for those that were in Sham if they choose, or those in real could choose to continue for another 2 weeks) 1 month follow up **Outcome ascertainment:** Baseline, week 2 **Type of Analysis:** Intention-to-treat
Loo[67] 2003, Australia	**Patient Selection:** Unknown **Inclusion Criteria:** DSM-IV major depressive episode, less than 2 years long, treatment resistant depression, ≥25 on the Montgomery-Asberg Depression Rating Scale **Exclusion Criteria:** physical or neurological disease, treated with ECT during current episode **Patient Selection:** Nine participants, (6 female, 3 male), mean age 54.9(18.03) received active rTMS. Ten participants (6 female, 4 male), mean age 48.4(10.88) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 1 adequate trial of antidepressants	**Type of Control** Sham with or without continued antidepressants (either tapered or remained in the ineffective antidepressants) **Type of Comparator** 15Hz rTMS delivered at 90% motor threshold for 24 sessions over 3 weeks.	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, CARE, Beck Depression Inventory, Hamilton Depression Rating Scale, AUSSI, Mini-mental State examinations, Rey Auditory Verbal learning Test, Tower of London, Controlled Oral Word Association Test, Expanded Paired Associate Test, visual learning **Follow-up time:** Seven weeks **Outcome ascertainment:** Baseline, week 3, 1 post-treatment **Type of Analysis:** Intention-to-treat
Loo[66] 2007, Australia	**Patient Selection:** Outpatients referred by psychiatrists or general practitioners **Inclusion Criteria:** DSM-IV diagnosis of major depressive episode, less than 2 years in length, ≥25 on the Montgomery-Asberg Depression Rating Scale, treatment resistant depression **Exclusion Criteria:** Axis 1 disorders, neurological illness, epilepsy, severe medical illness, implanted electronic devices, suicidal, or psychotic, patients that had failed more than 2 classes of antidepressants **Patient Selection:** Thirty-eight subjects randomly assigned (19 active, 21 sham). Nineteen participants (10 females, 9 males), mean age 49.8 (2.5) received active rTMS. Twenty-one participants (8 females, 11 males) mean age 45.7(15.0) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 1 adequate trial of antidepressants	**Type of Control** Sham with or without continued antidepressants (on medications that they had failed to respond to) **Type of Comparator** 10 Hz rTMS to the left dorsolateral prefrontal cortex delivered at 110% motor threshold, 5 second duration, 30 trains, 25 seconds between trains, for 2 times a day, separated by 2 hours over a period of 2 weeks	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, Hamilton Depression Rating Scale, CORE, Beck Depression Inventory, AUSSI, Rey auditory verbal learning test, Trail making test A and B, Wechsler Adult Intelligence Scale digit span, Controlled Oral Word Association Test. **Follow-up time:** 6 months post-rTMS **Outcome ascertainment:** Baseline, weekly, 1 month, and 6 month follow-up. Blind broken at 2 weeks.

			Type of Analysis: Intention-to-treat
Manes[53] 2001, United States	**Patient Selection:** Outpatients in Iowa City recruited through advertisement **Inclusion Criteria:** Major or minor depression as diagnosed by DSM-IV, treatment resistant, Caucasian, older than 50 years old **Exclusion Criteria:** Not reported **Patient Selection:** Ten participants (5 females, 5 males), mean age 60.35(3.4) received active rTMS. Ten participants (5 females, 5 males), mean age 60.9(2) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least one 4 week trial of the highest tolerated dose of antidepressant medication.	**Type of Control** Sham without medication **Type of Comparator** 20Hz rTMS delivered at 80% motor threshold, for 2 seconds x 20 trains, 1 minute between trains; for 5 days	**Outcomes measured:** Hamilton Depression Rating Scale, Mini-Mental State Exam, **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, daily, 1 week after last treatment **Type of Analysis:** Not reported
Mantovani[54] 2013, United States	**Patient Selection:** Brain behaviour clinic and the Anxiety Disorders Clinic of New York State Psychiatric Institute/Columbia University between January 2008 and December 2010 **Inclusion Criteria:** 18-65 years old, diagnosis of panic disorder and major depressive disorder confirmed with DSM-IV, lasting at least a month, treatment resistant, if patient is on medication must be stable for at least 4 weeks or psychotherapy for 3 months **Exclusion Criteria:** had acute suicide risk, history of bipolar disorder, psychotic disorder, substance abuse within the past year, neurological disorders, increase risk of seizure, implanted devised, metal in brain, unstable medical conditions, pregnant or breast feeding, prior rTMS **Patient Selection:** Twelve participants (8 female, 4 male), mean age 40.2(10) received active rTMS. Thirteen participants (5 female, 8 male), mean age 39.8(13.3) received sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least one adequate antidepressant trial	**Type of Control** Sham remaining on medication **Type of Comparator** 1 Hz rTMS to the right dorsolateral prefrontal cortex, delivered at 100% motor threshold in 30 min train (1800 pulses per day) 5 days a week for 4 weeks	**Outcomes measured:** PDSS and PDSS self-report, Hamilton Depression Rating Scale, HARS-14, Beck Depression Inventory-II, ZUNG-self-administered scale, Clinical Global Impression, PGI, Self-reported social adaptation scale **Follow-up time:** 6 months **Outcome ascertainment:** Baseline, weeks 2, 4, 6 months post-treatment **Type of Analysis:** Not reported
McDonald[55] 2006, United States	**Patient Selection:** Patients were recruited from the community (no dates specified). Randomization method was not specified. **Inclusion Criteria:** Hamilton Depression Rating Scale > 20 **Exclusion Criteria:** evidence of dementia on neuropsychological testing or meeting SCID criteria for Organic Brain Syndrome, Organic Mood Disorder, Substance Dependence within the last 6 months, a diagnosis of a significant central neurological disorders, pregnancy, the presence of cardiac pacemakers, cochlear implants, or other intracranial implants with the exception of dental fillings, presence of psychiatric symptoms of significant severity, requirement of continued treatment with antidepressant medications, acute, unstable medical conditions, previous TMS. **Patient Characteristics:** Twelve participants (7 males, 5 females), mean age 54 (SD not reported), were randomized to receive sham rTMS. Twenty-five patients with a mean age of 49.0 (SD not reported),18 females and 7 males received left-sided high frequency then right-sided low frequency rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 3 trials of antidepressants medications during the current episode	**Left-sided high frequency/right-sided low frequency:** 10Hz to the left DLPFC at 110% motor threshold for 20 trains (1000 pulses) followed by 1 Hz to the right DLPFC 110% motor threshold for 20 trains (600 pulses) for 5 days/week for 2 weeks	**Outcomes measured:** Hamilton Depression Rating Scale, Clinical Global Impression, Beck Depression Inventory, Brief Psychiatric Rating Scale **Follow-up time:** 3 months **Outcome ascertainment:** Baseline, week 2, month 1, month 2, month 3 **Type of Analysis:** Intention-to-treat

Moller[84] 2006, Iceland	**Patient Selection:** Participants were referred by psychiatrists from Landspitali-University Hospital, and randomized by coin toss **Inclusion Criteria:** Treatment resistant, diagnosis of depressive disorder based on ICD 10, had not received rTMS before, met published safety criteria for rTMS treatment **Exclusion Criteria:** Not reported **Patient Selection:** 10 patients (6 women and 4 men), average age 54 (14), randomized to 7 in active and 3 sham **Definition of Treatment Resistance:** Determined by referral psychiatrists	**Type of Control** Sham with sustained medication **Type of Comparator** 10Hz rTMS to the left prefrontal cortex, for 5 seconds x 40 trains, 25 seconds between trains; every day for 5 days with 4 weeks washout in between	**Outcomes measured:** Hamilton Depression Rating Scale, P_{300} **Follow-up time:** 4-6 weeks **Outcome ascertainment:** Baseline, 1 week after treatment **Type of Analysis:** Not Reported
Moser[56] 2002, United States	**Patient Selection:** Not reported **Inclusion Criteria:** Treatment resistant depression, 48-78 years **Exclusion Criteria:** Not reported **Patient Selection:** Nine participants, mean age 61.22[10.3] were randomized to receive active rTMS. Ten participants, mean age 60.9[10.2] were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Not reported	**Type of Control** Sham without medication **Type of Comparator** 20Hz rTMS to the left dorsolateral prefrontal cortex, delivered at 80% motor threshold, 2 second trains x20, 1min between trains; 5 sessions over 5 days	**Outcomes measured:** Hamilton Depression Rating Scale, Trail making Test A and B, Stroop Test, Controlled oral word association, Boston naming test, Rey Auditory Verbal Learning Test, Judgment of Line Orientation **Follow-up time:** 5 days **Outcome ascertainment:** Baseline, 5 days **Type of Analysis:** Not reported
Mosimann[57] 2004, United States	**Patient Selection:** Referred by general practitioners or psychiatrists **Inclusion Criteria:** 40-90 years old, diagnosis of treatment resistant depression according to DSM-IV and ICD-10 **Exclusion Criteria:** head injury, epilepsy, comorbid unstable medical or neurological illness, no birth control (women), **Patient Selection:** Forty-two patients referred, 18 excluded before patient randomization. Fifteen participants (5 female, 10 male), mean age 60 (13.4) received active rTMS. Nine participants (5 female, 4 male), mean age 64.4(13) received sham rTMS **Definition of Treatment Resistance:** Failure to respond to at least two adequate antidepressant trials during current depressive episode.	**Type of Control** Sham with antidepressant medication (remaining stable) **Type of Comparator** 20 Hz rTMS to the left dorsolateral prefrontal cortex delivered at 100% motor threshold in 2 second trains with 28 seconds between trains (1600 pulses), for 10 daily sessions over 2 weeks (5 per week)	**Outcomes measured:** Hamilton Depression Rating Scale, Beck Depression Inventory, National Institute of Mental Health Scale, Visual analogue scale, Mini-mental State exam, Verbal learning task, Stroop test, Trail-Making Tests A and B, word fluency test **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, week 2 **Type of Analysis:** Not reported
O'Reardon[58] 2007, United States	**Patient Selection:** Participants were recruited from twenty-three sites in United States, Australia, Canada, from January 2004 to August 2005 **Inclusion Criteria:** Medication free outpatient, age 18-70, DSM-IV diagnosis of Major Depressive Disorder, <3 year length of current episode, ≥4 Clinical Global Impression, ≥20 Hamilton Depression Rating Scale, symptom stability for 1 week, treatment resistant depression **Exclusion Criteria:** psychosis, bipolar disorder, obsessive compulsive disorder, posttraumatic stress disorder, eating disorder, no response to ECT, prior treatment with TMS, pregnant, personal or family history of seizures, neurologic disorder or medication that alters seizure threshold, ferromagnetic material in close proximity to head **Patient Selection:** 155 participants (86 females, 69 males), mean age 47.9(11) were randomized to receive active rTMS. 146 participants (74 females, 72 males), mean age 48.7(10.6) were randomized to receive sham rTMS **Definition of Treatment Resistance:** Failure to respond to 1-4 adequate trials of antidepressants	**Type of Control** Sham with no antidepressants **Type of Comparator** rTMS to the left dorsolateral prefrontal cortex delivered at 120% motor threshold, 10pulses a second, 4 seconds on at 26 second intervals; 6 weeks with 5 sessions per week (1 daily)	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, Hamilton Depression Rating Scale, Clinical Global Impression **Follow-up time:** 10 weeks **Outcome ascertainment:** Baseline, week 2, 4, and 6 **Type of Analysis:** Intention-to-treat
Padberg[90] 1999, Germany	**Patient Selection:** Right-handed patients from the Department of Psychiatry, Ludwig-Maximilian University Munich participated in the study. **Inclusion Criteria:** Patients who met the DSM-IV criteria for Major Depressive Disorder (single episode in three, recurrent depression in 15). **Exclusion Criteria:** Patients with organic brain disorders, pacemakers, mobile metal implants or implanted medication pumps were excluded.	**Type of Control** sham rTMS **Type of Comparator** Fast rTMS at 10 Hz administered as 5 trains of 5s duration (≥30 s intertrain interval). Stimulation was applied at 90% of MT, using 250 stimuli per day for 5 successive days from Monday (day 1) to Friday (day 5).	**Outcomes measured:** Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, Adjective Mood (Bf-Sr/Bf-S9) and Depression (D-SrD-S9) Scales, Verbal Learning Task. **Follow-up time:** 5 days

	Patient Characteristics: Eighteen patients (12 received rTMS) were included. Six patients were randomized to the sham rTMS group, 4 males and 2 females were, with a mean age of 63.5(15.8). Six patients were randomized to the high-frequency rTMS group, 2 women and 4 men, with a mean age of 63.5 ± 15.8 years. **Definition of Treatment Resistance:** Received at least two, 4-week trials of adequate antidepressant treatment, including one tricyclic antidepressant, without a therapeutic response.		**Outcome ascertainment:** Baseline and after the last rTMS treatment (day 5) **Type of Analysis:** Not reported
Padberg[76] 2002, Germany	**Patient Selection:** Patients from the Department of Psychiatry, Ludwig-Maximilian University Munich participated in the study. **Inclusion Criteria:** Patients who met the DSM-IV criteria for Major Depressive Disorder (single episode in three, recurrent depression in 15). **Exclusion Criteria:** Patients with organic brain disorders, pacemakers, mobile metal implants or implanted medication pumps were excluded. **Patient Characteristics:** Thirty-one patients (20 received rTMS) were included. Ten patients were randomized to the sham rTMS group, 8 females and 2 males, with a mean age of 52.7(5.7) years. Ten patients were randomized to the high-stimulation intensity group, 6 women and 4 men, with a mean age of 62.1 ± 4.6 years. **Definition of Treatment Resistance:** At least two antidepressant trials of adequate duration and dosage without significant clinical improvement.	**Type of Control** sham rTMS **Type of Comparator** 100% stimulation intensity related to MT (1500 stimuli/day, 10 Hz, 10 s, 15 trains, 30 s intertrain-interval). Patients underwent 10 afternoon sessions of rTMS at the left DLPFC within two weeks.	**Outcomes measured:** Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, Clinical Global Impression, VAS and brief questionnaires to document side effects, tolerability, and rTMS-induced sensations. **Follow-up time:** 14 days **Outcome ascertainment:** Before treatment (baseline), and at day 7 and day 14 of the study. **Type of Analysis:** Not reported
Paillère Martinot[83] 2010, France	**Patient Selection:** Patients were recruited by senior psychiatrists from consecutive admissions at five university psychiatry departments. **Inclusion Criteria:** Patients with a DSM-IV-R diagnosis of major depressive disorder. **Exclusion Criteria:** Age >65 yr, alcohol or substance dependence in the past 6 months, electroconvulsive therapy (ECT) treatment in the past 6 months, any present medical condition, history of epileptic seizures, history of neurological disorders or substantial brain damage, and contraindication to magnetic fields, according to established safety criteria. **Patient Characteristics:** Fifty patients (34 received rTMS) entered the study. Twenty patients were randomized to the standard rTMS group, 11 females and 9 males, with a mean age: 48.19 ± 7.77 years. Fourteen patients were randomized to the sham rTMS group, 10 females and 6 males, with a mean age of 46.57(10.27) years. **Definition of Treatment Resistance:** At least two trials of antidepressants of different classes given at adequate doses (>150 mg/d in an equivalent dose of imipramine) and duration (at least 4 wk for each drug).	**Type of Control:** Sham with stable doses of prior medication for at least 2 weeks **Type of Comparator:** rTMS target location was based on motor cortex location. Twenty trains of 8 s with 60-s inter-train intervals were administered with stimulus frequency at 10 Hz and intensity at 90% of MT, resulting in a total of 1600 pulses over 20 min. rTMS was administered on 10 consecutive working days, providing a total of 16000 impulses. While on a stable dose of prior medications	**Outcomes measured:** Montgomery-Asberg Depression Rating Scale, Hamilton Depression Rating Scale, and the Clinical Global Impression of Illness – Severity (CGI-S). **Follow-up time:** 10 days **Outcome ascertainment:** Baseline and the last day of treatment (Day 10). **Type of Analysis:** Intent-to-treat
Pascual-Leone[71] 1996, Spain	**Patient Selection:** Participants consisted of 17 right-handed patients either admitted to hospital or treated in an outpatient setting. **Inclusion Criteria:** Patients who met the diagnostic criteria for major depression psychotic subtype (DSM-III-R); met published safety criteria for rTMS; and gave their informed consent to the study. **Exclusion Criteria:** History of brain surgery or epilepsy; abnormal neurological and general physical examinations; concurrent serious medical illnesses requiring long-term treatment; previously received TMS. **Patient Characteristics:** Seventeen patients entered into the multiple cross-over study. None had bipolar affective disorder, but all had a history of relapsing unipolar major depression. Nine patients had previously received electroconvulsive treatment to which they had responded with significant benefit for several months. **Definition of Treatment Resistance:** At least three episodes of depression that had been resistant to multiple medications, despite combinations and high dosage.	**Type of Control:** Sham with or without antidepressant usage **Type of Comparator:** rTMS to the left DLPFC applied at different scalp positions. Five courses of rTMS were administered, each consisting of five sessions over 5 (consecutive) days. Each session consisted of 20 trains of 10 s duration separated by 1 min pauses. Stimulation was applied at 10 Hz frequency at 90% intensity of the patient's motor threshold.	**Outcomes measured:** Hamilton Depression Rating Scale and Beck's Questionnaire for patient self-rated mood. **Follow-up time:** 5 months **Outcome ascertainment:** Baseline and weekly throughout the study (i.e. at the end of weeks 1-20 of the study). **Type of Analysis:** Not reported

Peng[73] 2012, China	**Patient Selection:** Inpatient and outpatient units at Institute of Mental Health at Sexond Xiangya Hospital of Central South University **Inclusion Criteria:** Treatment resistant, met DSM-IV for major depressive episode, naïve to rTMS **Exclusion Criteria:** psychiatric axis 1 and 2 disorders, epileptic seizures, any neurological disorder, metal implants, other clinically relevant abnormalities **Patient Selection:** Seventeen participants (7 females, 10 males), mean age 27.4(6.145) were randomized to receive active rTMS. Thirteen participants (4 females, 9 males), mean age 26.380(3.452) were randomized to receive sham rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 2 different antidepressants given for 4 weeks each at the maximum recommended dose	**Type of Control** Sham with 10mg/day escitalopram **Type of Comparator** 15 Hz rTMS to the left dorsolateral prefrontal cortex at 110% motor threshold, 4 second duration of 50 trains, (3000 stimulations a day); 4 weeks with 20 sessions (5 per week). In addition to active rTMS, participants took 10mg/day escitalopram.	**Outcomes measured:** Beck Depression Inventory, Hamilton Depression Rating Scale **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, week 4 **Type of Analysis:** Not reported
Rossini[78] 2005, Italy	**Patient Selection:** Participants consisted of right-handed patients, consecutively admitted to the mood disorders center of the Department of Psychiatry (San Raffaele Hospital, Milan, Italy). **Inclusion Criteria:** Patients suffering from a severe (HAM-D score of 26 or higher) and drug-resistant major depressive episode without psychotic features established on the basis of unstructured clinical interviews and medical records according to DSM-IV criteria and following the best estimate procedure. **Exclusion Criteria:** Age younger than 18 years and older than 75 years, history of seizures or neurological illnesses, severe medical conditions that could interfere with the clinical evaluation, pregnancy, mental retardation, and Edinburgh Handedness Inventory score below +70, and patients bearing pacemakers, mobile metal implants, implanted medical pumps or metal clips placed inside the skull. **Patient Characteristics:** Fifty-two out of 54 patients enrolled, completed the entire study protocol. Eighteen patients were randomized to the high-intensity rTMS group, 12 females and 6 males, with a mean age of 57.4 ± 8.7 years. Seventeen patients (11 females, 6 males) with a mean age of 56.3(12.6) were randomized to receive sham rTMS. **Definition of Treatment Resistance:** A lack of improvement to at least two different treatments with antidepressants, at adequate dosage and duration, administered during the current episode.	**Type of Control:** Sham with stable medication **Type of Comparator:** rTMS stimulation intensity of 100% of MT, frequency 15 Hz and duration of the train of stimulations 2 s. The inter-train interval was 28 s, and every subject received 20 trains of pulses per session. Patients underwent 10 sessions of stimulation over a 2-week period (Monday to Friday).	**Outcomes measured:** Hamilton Depression Rating Scale, Clinical Global Impression (Severity and Improvement) **Follow-up time:** 5 weeks **Outcome ascertainment:** Baseline (with the exception of CGI-I) and weekly thereafter for 5 weeks. **Type of Analysis:** Not reported
Speer[59] 2009, United States	**Patient Selection:** Not reported **Inclusion Criteria:** Highly treatment-resistant depressed patients meeting DSM-IV criteria for either bipolar illness or unipolar major depression. **Exclusion Criteria:** Not reported **Patient Characteristics:** Twenty-two patients with either bipolar illness (n=9) or unipolar major depression (n=13) were included in the multiple cross-over study and 19 of these patients received both high- and low-frequency active rTMS. **Definition of Treatment Resistance:** Not reported	**Type of Control:** sham rTMS **Type of Comparator:** 20 Hz stimulation was administered with 2s on an d 28 s off, 40 times, for a total of 1600 stimulations per 20-minute session. Stimulation was applied over the left PFC at 100% of MT. Patients were first randomized to receive 10 daily sessions (five times/week) of a) high- or low-frequency active rTMS, or b) sham rTMS. Those receiving active rTMS were then crossed over to the opposite frequency in the second two weeks to evaluate response within individuals. Those receiving sham rTMS first were then exposed to both of the other rTMS frequencies for two weeks. After patients were exposed to both active frequencies, they were allowed to enter a continuation phase (at the rTMS frequency to which they had responded the best) for treatment confirmation and optimization.	**Outcomes measured:** Hamilton Depression Rating Scale (28-item expanded version). **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline and the end of weeks 1, 2, 3 and 4. **Type of Analysis:** Not reported

Speer[60] 2013, United States	**Patient Selection:** Participants were recruited from treatment resistant inpatients and outpatients. **Inclusion Criteria:** Patients diagnosed by SCID interview meeting DSM-IV criteria for major depressive episode that were treatment resistant. **Exclusion Criteria:** A history of seizure disorders or other major comorbid medical problems or psychiatric diagnoses, and not previously undergone ECT. **Patient Characteristics:** Twenty-four patients (16 received rTMS) presented with unipolar (n=15) or bipolar (n=9) depression were included. Eight patients were randomized to the sham rTMS group, 3 females and 5 males, with a mean age of 44.9(9.1) years. Eight patients were randomized to the high-frequency rTMS group, 5 females and 3 males, with a mean age of 41.3 ± 14.5 years. **Definition of Treatment Resistance:** Failed at least two previous antidepressant trials.	**Type of Control:** Sham **Type of Comparator:** 20 Hz stimulation was administered with 2s on and 28 s off, 40 times, for a total of 1600 stimulations/20 min session. Patients received 15 daily sessions of rTMS (five times/week) over the left PFC at 110% of MT.	**Outcomes measured:** Hamilton Depression Rating Scale (28-item expanded version). **Follow-up time:** 7 weeks: 3 weeks randomized, blind trial and 4 weeks of open treatment continuation. **Outcome ascertainment:** Baseline and weekly thereafter for 7 weeks. **Type of Analysis:** Not reported
Stern[61] 2007, United States	**Patient Selection:** Participants were outpatients who had been referred for ECT having failed an adequate course of antidepressant medication. **Inclusion Criteria:** Patients were right-handed, between the ages of 21 and 80, met the SCID and DSM-IV criteria for a major depressive episode (score of 20 on the HAM-D), had no psychotic features, no other Axis I were naïve to TMS, and not participated in previous research studies on TMS and depression. **Exclusion Criteria:** A history of any psychotic disorder, including schizophrenia or schizoaffective disorder; bipolar disorder; obsessive compulsive disorder; personality disorder; substance abuse (except nicotine) within past year; current acute or chronic medical condition requiring treatment with psychoactive medication; a history of epilepsy or unprovoked seizures or other neurological disorder; abnormal neurological examination; family history of medication-resistant epilepsy; prior brain surgery; metal in the head; an implanted medical device; pregnancy; or unable to tolerate the medication withdrawal (14-day washout period). **Patient Characteristics:** Sixty patients (30 received rTMS) with unipolar disorder were included. Fifteen patients were randomized to the sham rTMS group, 9 females and 6 males, with a mean age of 53.3(9) years. Ten patients were randomized to the left-sided high-frequency rTMS group, 6 females and 4 males, with a mean age of 53.2 ± 12 years. **Definition of Treatment Resistance:** Not reported	**Type of Control:** Sham without medication **Type of comparator:** Left-sided DLPFC rTMS at a frequency of 10 Hz, 20 train per session (8s train and 52s intertrain interval), duration of 1200s per session, and stimuli provided at 110% MT. Patients received rTMS treatment for 10 days.	**Outcomes measured:** Hamilton Depression Rating Scale (21-item). **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline and weekly thereafter for 4 weeks. **Type of Analysis:** Not reported
Su[74] 2005, China	**Patient Selection:** Not reported **Inclusion Criteria:** Patients who met the DSM-IV criteria for a major depressive episode or bipolar disorder (based on the Mini-International Psychiatric Interview), were treatment resistant. **Exclusion Criteria:** A history of epilepsy, history of physical or neurological abnormalities, an implanted pacemaker, showed any signs of substantial risk of suicide during the trial, or previously had major head trauma or displayed any psychotic symptoms, not previously had rTMS treatment or ECT. **Patient Characteristics:** Thirty patients (22 received rTMS) were included. Ten patients were randomized to the sham rTMS group, 7 females and 3 males, with a mean age of 42.6(11.0) years. Ten patients were randomized to the high-frequency rTMS group, 7 females and 3 males, with a mean age of 43.6 ± 12.0 years. **Definition of Treatment Resistance:** Failed to respond to at least two adequate trials of antidepressant medications (a minimum of 6 weeks of treatment with a dosage adequate for treatment of depression in the majority of patients) prior to rTMS treatment.	**Type of Control:** Sham **Type of Comparator:** 20 Hz stimulation to the left DLPFC, in 40 2-second trains over 20 mins for 10 weekdays (total= 16,000 pulses) at 100% MT.	**Outcomes measured:** Hamilton Depression Rating Scale (21-item), Clinical Global Impression – Severity, Beck Depression Inventory. **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline and weekly thereafter for 2 weeks. **Type of Analysis:** Not reported
Triggs[62] 2010, United States	**Patient Selection:** Participants were recruited through psychiatrists in private practice, referrals from tertiary care center clinics, and newspaper advertisements. **Inclusion Criteria:** Between 18 and 75 years of age, medically-resistant major depression according to DSM-IV criteria and verified by the SCID, and score of 18 or higher and a score of at least 3 on item number 1 of the 24-item HAM-D in two separate screening sessions. **Exclusion Criteria:** A lifetime history of schizophrenia, schizoaffective disorder, other functional psychosis, rapid-cycling bipolar illness, alcohol or drug abuse within the past year; a positive urine drug test; axis II diagnosis of Cluster A (paranoid, schizoid, or schizotypal) or Cluster B (antisocial, borderline, histrionic, or narcissistic) personality disorder or mental retardation; use of medications that may lower seizure threshold (e.g. metronidazole) if the particular medication could not be stopped or altered without affecting the patient's medical care; history of neurological illness, epilepsy or	**Type of Control:** Sham with medication **Type of Comparator:** Left rTMS at 100% to the DLPFC at 100% of MT at a rate of 5 Hz. Each daily treatment consisted of 2000 stimuli divided into 50 trains of 40 stimuli. Participants received 10 daily weekday sessions of either rTMS or sham rTMS over a 2-week period.	**Outcomes measured:** Hamilton Depression Rating Scale (24-item), Beck Depression Inventory, State Trait Anxiety Inventory **Follow-up time:** 3 months **Outcome ascertainment:** Baseline (3 separate occasions during the 2-week period prior to rTMS), weekly during the 2-week rTMS treatment period, and 1 week, 1-month and 3-months following completion of rTMS.

	seizure disorder, intracranial tumor, or major head trauma leading to loss of consciousness of any duration; evidence of central nervous system disease based on baseline complete neurological examination, EEG and contrast-enhanced computerized tomography or magnetic resonance imaging of the brain; history of implanted pacemaker or medication pump, metal plate in skull, or metal objects in the eye or skull; need for rapid clinical response due to conditions such as inanition, psychosis, or suicidality (defined as suicide attempt during the current major depressive episode or having a specific plan for committing suicide); a medical condition that was not well controlled, such as diabetes or hypertension, or concomitant medical or nutritional problems necessitating hospitalization; use of anticonvulsant mood stabilizers (e.g. carbamazepine, valproic acid); or inability to personally grant informed consent. **Patient Characteristics:** Seven patients were randomized to the sham rTMS group, 4 females and 3 males, with a mean age of 46.6(20.2) years. Eighteen patients were randomized to the left-sided rTMS group, 14 females and 4 males, with a mean age of 46.7 ± 15.3 years. **Definition of Treatment Resistance:** Failed historically to respond to at least two separate trials (minimum duration 4 weeks) of therapeutic dosages of antidepressant medication (including at least one SSRI) or were intolerant of at least three different antidepressant medications (including at least one SSRI).		**Type of Analysis:** Not reported
Zheng[75] 2010, China	**Patient Selection:** Unknown **Inclusion Criteria:** Treatment Resistant, DSM-IV diagnosis of major depressive episode, Age 18-37 years, naïve to rTMS **Exclusion Criteria:** axis-I or axis-II disorders, epileptic seizure or other neurologic disorder, metal implants, clinically relevant abnormalities, drug of alcohol abuse **Patient Characteristics:** 34 subjects randomized to 19 active with 12 males and 7 females(mean age 26.9[6.2]), and 15 sham with 10 males and 5 females (mean age 26.7[4.3]) **Definition of Treatment Resistance:** Failure to respond to more than 2 antidepressants given at an adequate dosage for no longer than 4 weeks	**Type of Control** Sham taking escitalopram 10mg per day, not discontinuing antidepressants **Type of Comparator** 15 Hz 110% motor threshold, over the dorsolateral prefrontal cortex, 20 sessions over 4 weeks (3000 stimuli/day) taking escitalopram 10mg per day, not discontinuing antidepressants	**Outcomes measured:** Hamilton Depression Rating Scale, Beck Depression Inventory **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, week 4 **Type of Analysis:** Not reported

DLPFC Dorsolateral Prefrontal Cortex; **DSM** Diagnostic and Statistical Manual; **ECT** Electroconvulsive Therapy; **HAMD** Hamilton Depression Rating Scale; **Hz** Hertz; **rTMS** Repetitive Transcranial Magnetic Stimulation; **SD** Standard Deviation; **SSRI** Selective Serotonin Reuptake Inhibitor

5.3.4.2 Quality of Included Studies

Each of the RCTs comparing rTMS and sham had areas where the risk of bias was low and unclear (**Table 8**). There were only four studies which were assessed as having a high risk of bias in one of the seven areas. All of the included studies used some type of randomization to allocate patients to arms. However, most of the included studies did not report the method of randomization, and therefore it was not possible to assess random sequence generation. Due to unclear methods of random sequence generation, it was difficult to assess allocation concealment, and many received an unclear risk of bias in this area.

Generally, blinding of personnel, assessors and participants was clearly reported and the risk of bias introduced by blinding was low. All of the included studies except three used a blind outcome assessor; of the remaining three, two were not clear on whether the assessor was blind and another had a high risk of bias in this area due to not having a blinded assessor.

All included studies had complete outcome data (making the risk of bias due to incomplete data outcome low), and showed no evidence of selective reporting, with the exception of Bakim et al.[79], Pascual-Leone et al.[71] and Speer et al.[60] It is unknown whether other biases influenced the results of these studies. Due to this, "unclear risk of bias" was assigned to all included studies under the category "Other Bias."

Table 8: Quality Assessment of rTMS versus Sham Studies as Assessed by the Cochrane Risk of Bias[35]

Author	Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Any Other Bias?
Avery[42]	1999	Low	Low	Low	Low	Low	Low	Unclear
Avery[43]	2006	Low	Low	Low	Low	Low	Low	Unclear
Baeken[80]	2013	Low	Low	Low	Low	Low	Low	Unclear
Bakim [79]	2012	Low	Unclear	Unclear	Low	Low	High	Unclear
Bares[81]	2009	Low	Low	Low	Low	Low	Low	Unclear
Berman[85]	2000	Unclear	Unclear	Low	Low	Low	Low	Unclear
Blumberger[41]	2012	Low	Unclear	Unclear	Low	Low	Low	Unclear
Bortolomasi[77]	2007	Unclear	Unclear	Low	Low	Low	Low	Unclear
Boutros[45]	2002	Unclear	Unclear	Low	Low	Low	Low	Unclear
Bretlau[91]	2008	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
Chen[72]	2013	Unclear	Unclear	Low	Low	Low	Low	Unclear
Fitzgerald[63]	2003	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Fitzgerald[64]	2006	Low	Low	Low	Low	Low	Low	Unclear
Fitzgerald[65]	2012	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Garcia-Toro[68]	2001	Unclear	Unclear	Low	Low	Low	Low	Unclear
Garcia-Toro[69]	2006	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
George[46]	2010	Low	Low	Low	Low	Low	Low	Unclear
Hernandez-Ribas[70]	2013	Unclear	Unclear	Low	Low	Low	Low	Unclear
Holtzheimer[86]	2004	Unclear	Unclear	Low	Low	Low	Low	Unclear
Jorge[49]	2004	Unclear	Unclear	Low	Low	Low	Low	Unclear
Jorge[48]	2008	Unclear	Unclear	Low	Low	Low	Low	Unclear
Kauffmann[50]	2004	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Lisanby[51]	2009	Unclear	Unclear	Low	Low	low	Low	Unclear
Loo[52]	1999	Unclear	Unclear	Low	Low	Low	Low	Unclear
Loo[67]	2003	Unclear	Unclear	Low	Low	Low	Low	Unclear
Loo[66]	2007	Unclear	Unclear	Low	Low	Low	Low	Unclear
Manes[53]	2001	Unclear	Unclear	Low	Low	Low	Low	Unclear
Mantovani[54]	2013	Unclear	Unclear	Low	Low	Low	Low	Unclear
McDonald [55]	2006	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Moller[84]	2006	Low	Low	Low	Low	Low	Low	Unclear
Moser[56]	2002	Unclear	Unclear	Low	Low	Low	Low	Unclear
Mosimann[57]	2004	Unclear	Unclear	Low	Low	Low	Low	Unclear
O'Reardon[87]	2007	Unclear	Unclear	Low	Low	Low	Low	Unclear
Padberg [90]	1999	Unclear	Unclear	Unclear	Low	Low	Low	Unclear

Padberg [76]	2002	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Paillere Martinot[83]	2010	Low	Low	Unclear	Low	Low	Low	Unclear
Pascual-Leone[71]	1996	Unclear	Unclear	Unclear	Low	Low	High	Unclear
Peng[73]	2012	Unclear	Unclear	Low	Low	Low	Low	Unclear
Rossini[92]	2005	Low	Unclear	Unclear	Low	Low	Low	Unclear
Speer[59]	2009	Unclear	Unclear	Unclear	Low	Low	High	Unclear
Speer[60]	2013	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Stern[61]	2007	Unclear	Unclear	Low	Low	Low	Low	Unclear
Su[74]	2005	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Triggs[93]	2010	Low	Unclear	Unclear	Low	Low	Low	Unclear
Zheng[75]	2010	Unclear	Unclear	Low	High	Low	Low	Unclear

5.3.4.3 Meta-analysis of Treatment Response

Thirty-one of the rTMS versus sham studies provided adequate data on treatment response to permit pooling. **Figure 3** shows the response results (forest plot) for rTMS compared to sham. The definition of response as defined by the author was used in this analysis. Therefore, the scale and threshold for response varied by paper, as shown in the **Figure 3**. Four of these studies used the MADRS to define response, while the remaining twenty-seven studies used the HAMD to determine response. All of the papers using the HAMD used a cut off of at least 50% reduction in depression score. Two of the four studies using the MADRS to define response used a cut-off of at least 20% to define response, while the other two studies used a cut off of 50%.

The overall pooled risk ratio for rTMS versus sham is 2.35 (95% Confidence Interval [CI]: 1.70-3.25). This pooled estimate suggests that patients are twice as likely to experience treatment response with rTMS than with a sham procedure.

The pooled studies were assessed for risk of publication bias using a Begg's funnel plot (**Figure 4**). This funnel plot is largely symmetrical, with points located equally along the x and y axes of the graph (p=0.55). This suggests that the risk of publication bias is low.

Figure 3: Forest Plot of Response in Patients Receiving rTMS versus those receiving Sham Treatment

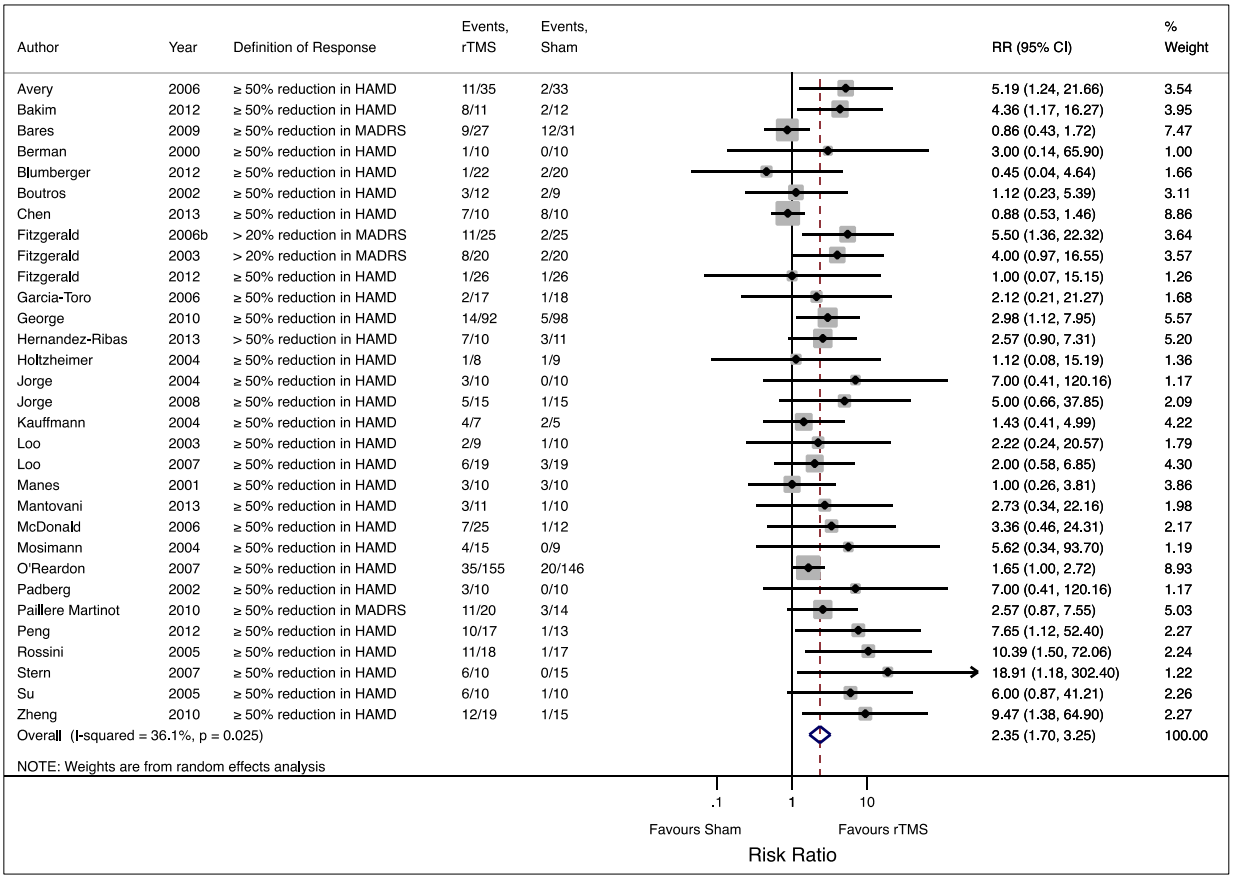
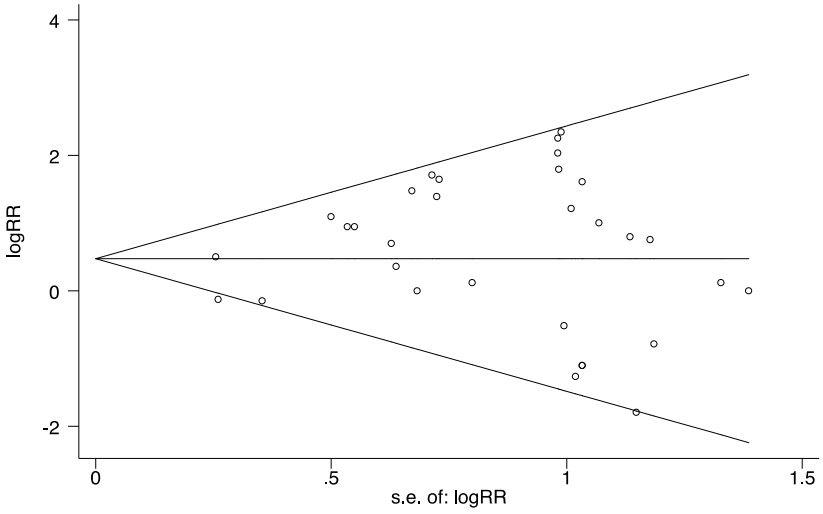


Figure 4: Beggs Funnel Plot with 95% Confidence Intervals to Test for Publication Bias in rTMS versus Sham Studies (Response)



5.3.4.4 Meta-analysis of Treatment Remission

Eighteen of the rTMS versus sham studies provided adequate data on treatment remission to permit pooling. **Figure 5** shows the remission results (forest plot) for rTMS compared to sham. The definition of remission as defined by each paper's authors was used in this analysis. Therefore, the scale remission varied by paper. Three of these studies used the MADRS to define remission, while the remaining studies used the HAMD. The threshold score used to define remission varied between 3 and 10. One study used a threshold of 3 to define remission[46], two used a threshold of 7[55;79], seven used a threshold of 8[43;48;49;53;74;78;87], and seven used a threshold of 10[41;50;54;61;64;66;81].

The overall pooled risk ratio for rTMS versus sham remission rate is 2.24 (95% CI: 1.53-3.27). This pooled estimate suggests that patients are twice as likely to experience remission with rTMS than with a sham procedure.

The pooled studies were assessed for risk of publication bias using a Begg's funnel plot (**Figure 6**). This funnel plot is largely symmetrical, with points located equally along the x and y axes of the graph. However, the p-value is 0.025, indicating that there may be evidence of some publication bias.

Figure 5: Forest Plot of Remission in Patients Receiving rTMS versus those receiving Sham Treatment

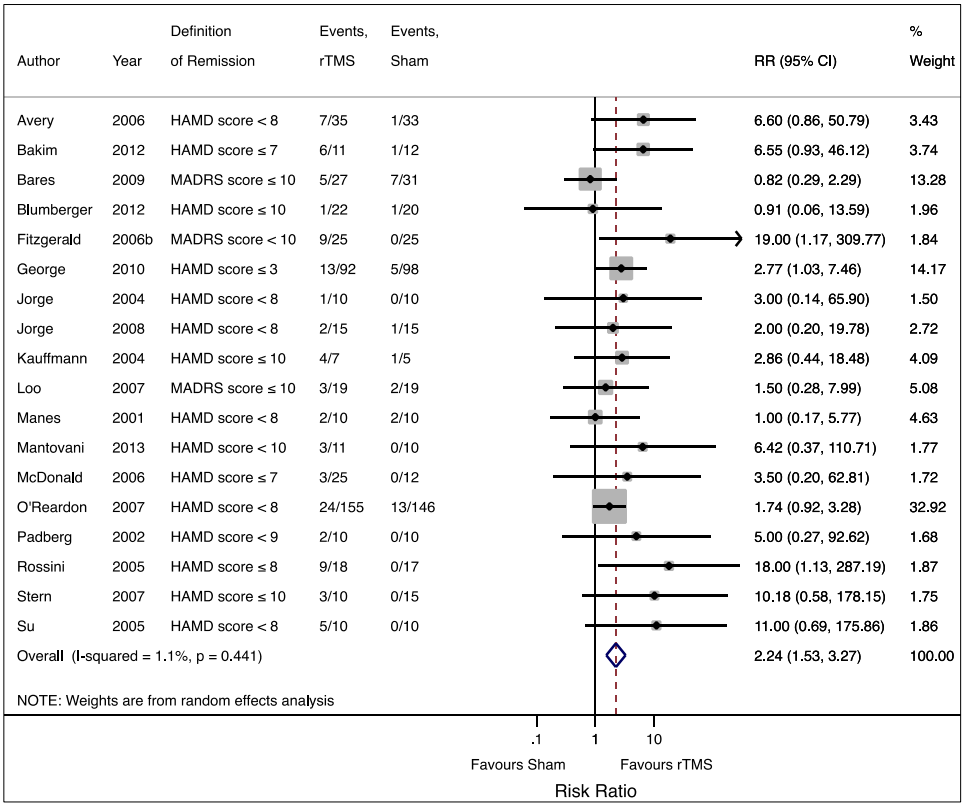
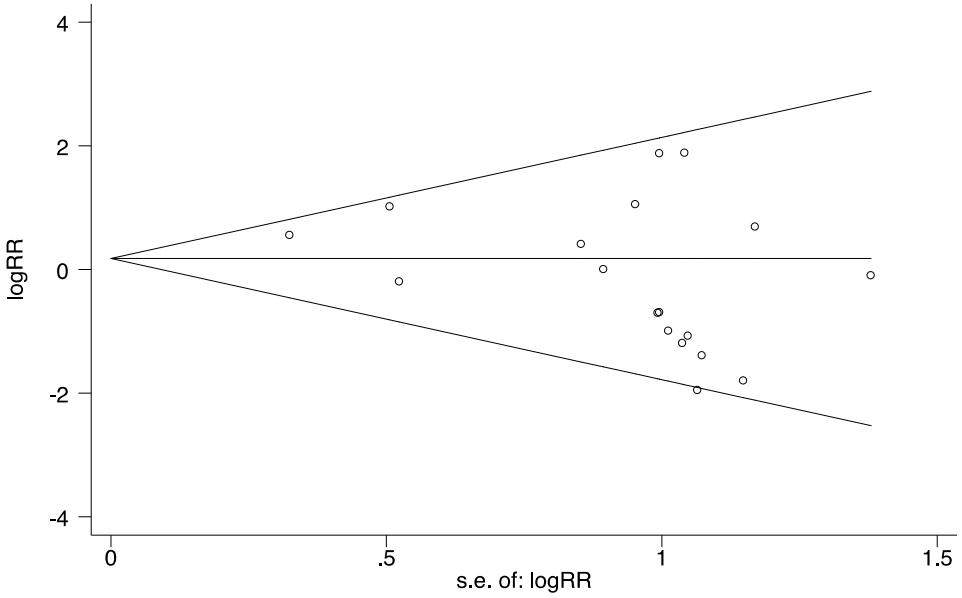


Figure 6: Beggs Funnel Plot with 95% Confidence Intervals to Test for Publication Bias in rTMS versus Sham Studies (Remission)



5.3.4.5 Safety of Repetitive Transcranial Magnetic Stimulation compared to Sham

The most frequently reported adverse effects in the forty-five studies assessing rTMS versus sham were pain/discomfort and headache. Ten studies reported that some of their patients had headaches[44;46;48;53;57;64;66;67;80;84]; all reported that the headaches subsided quickly. Although headaches were more common in the rTMS groups (in one study, 60% of participants in the rTMS group reported having a headache[44]), they also occurred in the sham groups (with up to 50% of the control group experiencing a headache[44]). Nine studies reported rates of patient discomfort or pain[42;43;45;46;48;53;57;66;67]. In six of these studies, discomfort and pain were reported in both the rTMS and sham groups[42;43;45;46;48;53]; the remaining three studies reported only pain/discomfort in the active group[57;66;67]. None of the included studies assessed serious adverse events such as cognitive impairment, seizures or suicide ideation.

5.3.4.6 Conclusions on Repetitive Transcranial Magnetic Stimulation Compared to Sham

rTMS is an effective treatment when compared to sham. Patients undergoing rTMS are twice as likely to achieve either clinical response or remission compared to patients undergoing a sham procedure. The most common side effects were headaches and pain/discomfort, which were reported in both rTMS and control groups. Major adverse events were not assessed in the included studies.

5.3.5 High Frequency Repetitive Transcranial Magnetic Stimulation Compared to Low Frequency Repetitive Transcranial Magnetic Stimulation

5.3.5.1 Characteristics of Included Studies

Fourteen of the included RCTs assessed the efficacy of high frequency rTMS compared to low frequency rTMS. The characteristics of each of these included studies have been summarized in **Table 9**. Four of the studies were conducted in the United States[59-61;94], four were conducted in Australia[63;95-97], two were conducted in both France[98;99] and in Italy[100;101], one study was conducted in China[74], and one in Germany[90]. The studies were published between 1999[90] and 2013[60]. None of the included studies reported whether they used an intention-to-treat analysis or a per-protocol analysis.

The protocol used for rTMS varied amongst the included studies. Frequency of rTMS used varied from 0.3 to 1 hertz (Hz) in the low frequency arms, and from 2 to 20 in the high frequency comparator arms. Motor threshold varied from 90% to 120%. Number of rTMS sessions provided to each participant varied from 5 to 20, over a period of 5 days to 4 weeks.

The definition of treatment resistant did not vary widely amongst the included studies. Of the studies that reported their definition of treatment resistance, all used a cut off of at least 2 adequate antidepressant trials. Four of the included studies did not report the threshold they used to define treatment resistance[59;61;100;101].

Table 9: Characteristics of Studies Assessing Efficacy of High Frequency rTMS versus Low Frequency rTMS

Author, Year of Publication, Country	*Patient Selection*	*Comparators*	*Outcomes*
Eche[99] 2012, France	**Patient Selection:** Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** MADRS score > 20 despite prescription of an anti-depressant for at least 12 weeks. **Exclusion Criteria:** History of personal or family seizures, neurological or neurosurgical antecedent, inner ear prosthesis, pace-maker, and anticonvulsive medication. **Patient Characteristics:** Eight patients with mean age of 46.1 (16.3), 6 females and 2 males were randomized to low frequency. Six patients with a mean age of 50.8 (9.4), 2 females and 4 males were randomized to high frequency. **Definition of Treatment Resistance:** Stage 1 of treatment-resistant depression.	**Low:** 1 HZ rTMS to right DLPFC 100% MT for 2 trains of 120 pulses once per day for 2-4 weeks. **High:** 10 HZ rTMS to left DLPFC 100% MT for 40 trains of 2000 pulses once per day for 2-4 weeks.	**Outcomes measured:** MADRS **Follow-up time:** 20 sessions (between 2-4 weeks) **Outcome ascertainment:** Baseline and every 5 sessions **Type of Analysis:** NR
Fitzgerald[63] 2003, Australia	**Patient Selection:** Patients were recruited from 2 outpatient clinics and by psychiatrist referral between October 2000 and September 2002 and were randomized via sealed envelopes. **Inclusion Criteria:** NR **Exclusion Criteria:** Significant medical illness, neurologic disorders or other Axis I psychiatric disorders. **Patient Characteristics:** Twenty patients with a mean age of 45.5 (11.49), 7 females and 13 males were randomized to low frequency right-sided rTMS. Twenty patients with a mean age of 42.2 (9.8), 8 females and 12 males were randomized to high frequency left-sided rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks.	**Low:** 1 Hz rTMS to right DLPFC 100% MT for 5 trains (300 stimuli per treatment) 5 days per week for 2 weeks. **High:** 10 Hz rTMS to left DLPFC 100% MT for 20 trains (1000 stimuli per treatment) 5 days per week for 2 weeks.	**Outcomes measured:** MADRS, BDI, BPRS, CORE rating of psychomotor disturbance, CGI, Personal Semantic Memory Schedule, Autobiographical Wechsler Adult Intelligence Scale, Tower of London, Controlled Oral Word Association Test **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks, 4 weeks **Type of Analysis:** NR
Fitzgerald[97] 2006a, Australia	**Patient Selection:** Patients were recruited from 3 hospitals between May 2004 and January 2006 and were randomized using computer generated sequences. **Inclusion Criteria:** HAMD score > 16 **Exclusion Criteria:** Significant medical illness, neurologic disorders, contraindications to rTMS, DSM-IV diagnosis of alcohol or substance dependence. **Patient Characteristics:** Sixty-seven patients with a mean age of 50.5 (13.8), 45 females and 22 males were randomized to low frequency rTMS. Sixty-three patients with a mean age of 48.1 (14.0), 38 females and 25 males were randomized to high frequency rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode.	**Low:** 1 Hz rTMS to right DLPFC 110% MT for 1 train (900 stimuli per treatment) 5 days per week for 2 weeks. **High:** 2 Hz rTMS to right DLPFC 110% MT for 1 train (1800 stimuli per treatment) 5 days per week for 2 weeks.	**Outcomes measured:** HAMD, BDI **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks, 4 weeks. **Type of Analysis:** NR
Fitzgerald[96] 2007, Australia	**Patient Selection:** Patients were recruited between March 2003 and January 2005 and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** NR **Patient Characteristics:** Eleven patients with a mean age of 39.6 (10), 5 females and 6 males were randomized to low frequency right-sided rTMS. Fifteen patients with a mean age of 42.4 (11.2), 8 females and 7 males were randomized to high frequency left-sided rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode.	**Low:** 1 Hz rTMS to right DLPFC 110% MT for 4 trains, 5 days per week for 3 weeks. **High:** 10 Hz rTMS to left DLPFC 100% MT for 30 trains, 5 days per week for 3 weeks.	**Outcomes measured:** MADRS **Follow-up time:** 3 weeks **Outcome ascertainment:** Baseline, 3 weeks **Type of Analysis:** NR

Fitzgerald[95] 2009b, Australia	**Patient Selection:** Patients were recruited from 1 outpatient clinic and by referral from private psychiatrists (recruitment dates not reported) and were randomized using computer generation. **Inclusion Criteria:** NR **Exclusion Criteria:** NR **Patient Characteristics:** Eleven patients with a mean age of 46.5 (11.4), 3 females and 8 males were randomized to low frequency right DLPFC rTMS. Fifteen patients with a mean age of 42.1 (9.3), 8 females and 7 males were randomized to high frequency left DLPFC rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode	**Low:** rTMS to the right DLPFC 110% MT for 4 trains 180 seconds duration 5 days per week for 3 weeks (HZ not specified). **High:** rTMS to the left DLPFC 100% MT for 30 trains 5seconds duration 5 days per week for 3 weeks (HZ not specified).	**Outcomes measured:** MADRS, BDI, HAMD, BPRS, CORE rating of psychomotor disturbance, GAF, Hopkins verbal learning test, controlled oral word association test, Digit span, Brief visuospatial memory test-revised. **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 3 weeks, 4 weeks **Type of Analysis:** NR
Isenberg[94] 2005, United States	**Patient Selection:** Patients were recruited through community physicians (recruitment dates not reported) and allocated to treatment based on date of entry. **Inclusion Criteria:** NR **Exclusion Criteria:** Psychosis, significant medical illnesses, neurologic disorders, implanted metal devices, or other major Axis I psychiatric disorders. **Patient Characteristics:** Fourteen patients with a mean age of 55.6 (9.7), 8 females and 6 males received right-sided low frequency rTMS. Fourteen patients with a mean age of 43.4 (9.7), 8 females and 6 males received left-sided high frequency rTMS. **Definition of Treatment Resistance:** Failed to respond to at least 2 treatment trials of different antidepressant medication types, each used for an adequate period of time at an adequate dose.	**Low:** 1 Hz rTMS to the right DLPFC at 110% MT for 2 trains 5 days/week for 4 weeks. **High:** 20 Hz rTMS to the left DLPFC at 80% MT for 50 trains of 40 pulses 5 days/week for 4 weeks.	**Outcomes measured:** HAMD, BDI, CGI, SSTAI, MMSE, Cloninger's Temperament and Character Inventory **Follow-up time:** 10 sessions (up to 4 weeks) **Outcome ascertainment:** Baseline, 5 sessions, 10 sessions. **Type of Analysis:** NR
Miniussi[101] 2005, Italy	**Patient Selection:** Patients were recruited from 1 hospital (recruitment dates not reported) and randomized (method not reported). **Inclusion Criteria:** HAMD score $\geq$ 12 or clinical improvement on the HRSD $\leq$ 50% obtained after treatment with at least two classes of anti-depressive drugs, no history of epilepsy or other neurological disorders. **Exclusion Criteria:** NR **Patient Characteristics:** Twenty inpatients (15 female and 5 male) were included in the first experimental treatment. Ten patients with a mean age of 52 years received low-frequency rTMS. Ten patients with a mean age of 58 years received left-sided high-frequency rTMS. Forty outpatients were included in the second experimental treatment. Twenty patients with mean age ranging from 48-59 years, received low-frequency rTMS group. Twenty patients with mean age ranging from 53-54 years, received high-frequency rTMS group. **Definition of Treatment Resistance:** NR	**Low:** 1 Hz rTMS to the left DLPFC at 110% of MT for two experimental treatments. Experimental Treatment 1: 1 Hz rTMS (real/sham) of 5 consecutive sessions that started on Monday, separated by 24 hrs. Experimental Treatment 2: Patients received either a) real 1 Hz-TMS, followed by a second block of sham 1 Hz-TMS; or b) sham 1 Hz-rTMS first, followed by real 1 Hz-TMS second. The two blocks of stimulation (real/sham or sham/real) were separated by an interval of 8 weeks. **High:** 17 Hz rTMS to left DLPFC at 110% of MT for two experimental treatments. Experimental Treatment 1: 17 Hz-TMS (real/sham) of 5 consecutive sessions that started on Monday, separated by 24 hrs. Experimental Treatment 2: Patients received either a) real 17 Hz-TMS, followed by a second block of sham 17 Hz-TMS; or b) sham 17 Hz-rTMS first, followed by real 17 Hz-TMS second. The two blocks of stimulation (real/sham or sham/real) were separated by an interval of 8 weeks.	**Outcomes measured:** HAMD, BPRS. **Follow-up time:** 1 week for the first experimental treatment. 10 weeks for the second experimental treatment. **Outcome ascertainment:** Baseline, 5 days after treatment for the first experimental treatment. Baseline, 5 days, 8 weeks and 9 weeks after the first treatment block for the second experimental treatment **Type of Analysis:** NR

Padberg[90] 1999, Germany	**Patient Selection:** Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** Patients with organic brain disorders, pacemakers, mobile metal implants or implanted medication pumps were excluded. **Patient Characteristics:** Six patients with a mean age of 46.7 (14.7), 5 females and 1 male were randomized to the low-frequency rTMS group. Six patients with a mean age of 63.5 (15.8), 2 females and 4 males were randomized to the high-frequency rTMS group. **Definition of Treatment Resistance:** Received at least two, 4-week trials of adequate antidepressant treatment, including one tricyclic antidepressant, without a therapeutic response.	**Low:** 0.3 Hz rTMS to left DLPFC at 90% of MT for 10 trains of 25 pulses, 250 stimuli per day for 5 successive days from Monday (day 1) to Friday (day 5). **High-frequency:** 10 Hz rTMS to left DLPFC at 90% of MT for 5 trains of 5s duration, 250 stimuli per day for 5 successive days from Monday (day 1) to Friday (day 5).	**Outcomes measured:** HAMD, MADRS, Adjective Mood and Depression (D-S/D-S') Scales, Verbal Learning Task. **Follow-up time:** 5 days **Outcome ascertainment:** Baseline and after the last rTMS treatment (day 5) **Type of Analysis:** NR
Richieri[98] 2012, France	**Patient Selection:** Patients were screened through retrospective chart reviews from 1 teaching hospital from January 2010, to August 2010 and September 2010 to December 2010. **Inclusion Criteria:** Met the DSM-IV criteria for major depressive disorder (unipolar or bipolar depression). **Exclusion Criteria:** Age under 18 years, neurological disorders or convulsive disorders, and previous rTMS or ECT treatments. **Patient Characteristics:** Twenty-eight patients with a mean age of 54.1 (12.8), 14 females and 14 males were randomized to the low-frequency rTMS group,,Thirty-three patients with a mean age of 55.6 (12.5), 18 females and 15 males were randomized to the high-frequency rTMS group. **Definition of Treatment Resistance:** Not responsive to pharmacological treatment of depression using a minimum of two distinctly different classes of antidepressant medications for episodes occurring at the time of enrolment or earlier.	**Low:** 1 Hz rTMS to right DLPFC at a frequency at 120% of left MT, 60-second trains with a 30-second inter-train interval (360 pulses per day). Twenty treatment sessions were administered in a 4-week period (five sessions per week). **High:** 10 Hz rTMS to left DLPFC at 120% of right MT, 5-second trains with a 25-second inter-train interval (2000 pulses per day). Twenty treatment sessions were administered in a 4-week period (five sessions per week).	**Outcomes measured:** BDI,,CGI, STAI. **Follow-up time:** 4 weeks **Outcome ascertainment:** Twice at baseline and after 20 sessions (Week 4). **Type of Analysis:** NR
Rossini[100] 2010, Italy	**Patient Selection:** Patients consecutively admitted to 1 hospital were recruited from September 2006 to November 2007 and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** The presence of any concomitant axis I diagnosis, psychotic features, somatic or neurological illnesses impairing psychiatric evaluation, age younger than 18 years and older than 80 years, pregnancy, HAMD score less than 21, no history of seizures or bearing pacemakers, mobile metal implants, implanted medical pumps or metal clips placed inside the skull. **Patient Characteristics:** Forty-two patients with a mean age of 56.1 (13.1) for those with unipolar depression and 52.8 (10.7) for those with bipolar depression, 30 females and 12 males were randomized to the low-frequency rTMS group, Thirty-two patients with a mean age of 56.4 (8.9) for those with unipolar depression and 51.4 (14.1) for those with bipolar depression, 23 females and 9 males were randomized to the high-frequency rTMS group. ,. **Definition of Treatment Resistance:** NR	**Low:** 1 Hz rTMS to right DLPFC, 2 trains of 300 pulses for a total of 600 pulses/day. Stimulation was performed for 10 consecutive working days from Monday to Friday for 2 weeks (MT not reported). . **High:** 15 Hz rTMS to left DLPFC, 20 trains of 30 pulses (2sec each, with a 29sec intertrain interval), for a total or 600 pulses/day. Stimulation was performed for 10 consecutive working days from Monday to Friday for 2 weeks (MT not reported).	**Outcomes measured:** HAMD **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline and weekly thereafter for 2 weeks. **Type of Analysis:** NR
Speer[59] 2009, United States	**Patient Selection:** NR **Inclusion Criteria:** NR **Exclusion Criteria:** NR **Patient Characteristics:** Twenty-two patients with either bipolar illness (n=9) or unipolar major depression (n=13) were included in the multiple cross-over study and 19 of these patients received both high- and low-frequency active rTMS. **Definition of Treatment Resistance:** NR	**Low:** 1 Hz rTMS to left PFC at 100% of MT, given in a continuous train of 1600 pulses over 26 min 40s. **High:** 20 Hz rTMS to left PFC at 100% of MT, 2s on and 28 s off, 40 times, for a total of 1600 stimulations per 20-minute session.	**Outcomes measured:** HAMD expanded version (HAMD-28). **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline and the end of weeks 1, 2, 3 and 4. **Type of Analysis:** NR

		Patients were first randomized to receive 10 daily sessions (five times/week) of a) high- or low-frequency active rTMS, or b) sham rTMS. Those receiving active rTMS were then crossed over to the opposite frequency in the second two weeks to evaluate response within individuals. Those receiving sham rTMS first were then exposed to both of the other rTMS frequencies for two weeks. After patients were exposed to both active frequencies, they were allowed to enter a continuation phase (at the rTMS frequency to which they had responded the best) for treatment confirmation and optimization.	
Speer[60] 2013, United States	**Patient Selection:** Patients were recruited between October 2000 and April 2003 and were randomized (method not reported)**.** **Inclusion Criteria:** NR **Exclusion Criteria:** A history of seizure disorders or other major comorbid medical problems or psychiatric diagnoses, and not previously undergone ECT. **Patient Characteristics:** Eight patients with a mean age of 39.6 (9.0), 5 females and 3 males were randomized to the low-frequency rTMS group. Eight patients with a mean age of 41.3 (14.5), 5 females and 3 males were randomized to the high-frequency rTMS group. **Definition of Treatment Resistance:** Failed at least two previous antidepressant trials.	**Low:** 1 Hz rTMS to the left PFC at 110% of MT was given in a continuous train of 1,600 pulses over 26 min, 40 s. Patients received 15 daily sessions of rTMS (5-times/week). **High:** 20 Hz to the left PFC at 110% of MT was administered with 2s on and 28 s off, 40 times, for a total of 1600 stimulations/20 min session. Patients received 15 daily sessions of rTMS (5-times/week) over.	**Outcomes measured:** HAMD expanded version (HAMD-28). **Follow-up time:** 7 weeks **Outcome ascertainment:** Baseline and weekly thereafter for 7 weeks. **Type of Analysis:** NR
Stern[61] 2007, United States	**Patient Selection:** Patients were recruited from outpatients of 1 teaching hospital (recruitment dates not reported) who had been referred for ECT having failed an adequate course of antidepressant medication and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** A history of any psychotic disorder, including schizophrenia or schizoaffective disorder; bipolar disorder; obsessive compulsive disorder; personality disorder; substance abuse (except nicotine) within past year; current acute or chronic medical condition requiring treatment with psychoactive medication; a history of epilepsy or unprovoked seizures or other neurological disorder; abnormal neurological examination; family history of medication-resistant epilepsy; prior brain surgery; metal in the head; an implanted medical device; pregnancy; or unable to tolerate the medication withdrawal (14-day washout period). **Patient Characteristics:** Ten patients with a mean age of 52.3 (9.4), 6 females and 4 males were randomized to the left-sided low-frequency rTMS group. Ten patients with a mean age of 52.8 (9.5), 7 females and 3 males were randomized to the right-sided low-frequency rTMS group. Ten patients with a mean age of 53.2 (12), 6 females and 4 males were randomized to the left-sided high-frequency rTMS group. **Definition of Treatment Resistance:** NR	**Low A:** 1 Hz rTMS to left DLPFC at 110% MT, 1 train per session, duration of 1600s. Patients received rTMS treatment for 10 days. **Low B:** 1 Hz rTMS to right DLPFC at 110% MT, 1 train per session, duration of 1600s. Patients received rTMS treatment for 10 days. **High:** 10 Hz rTMS to left DLPFC rTMS at 110% MT, 20 train per session (8s train and 52s intertrain interval), duration of 1200s per session. Patients received rTMS treatment for 10 days.	**Outcomes measured:** HAMD **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline and weekly thereafter for 4 weeks. **Type of Analysis:** NR

Su[74] 2005, Taiwan	**Patient Selection:** Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** A history of epilepsy, history of physical or neurological abnormalities, an implanted pacemaker, showed any signs of substantial risk of suicide during the trial, or previously had major head trauma or displayed any psychotic symptoms, not previously had rTMS treatment or ECT. **Patient Characteristics:** Ten patients with a mean age of 43.2 (10.6), 8 females and 2 males were randomized to the low-frequency rTMS group. Ten patients with a mean age of 43.6 (12.0), 7 females and 3 males were randomized to the high-frequency rTMS group. **Definition of Treatment Resistance:** Failed to respond to at least two adequate trials of antidepressant medications (a minimum of 6 weeks of treatment with a dosage adequate for treatment of depression in the majority of patients) prior to rTMS treatment.	**Low:** 5 Hz rTMS to left DLPFC at 100% MT, in 40 8-second trains over 20 mins for 10 weekdays (total= 16,000 pulses)**.** **High:** 20 Hz rTMS to left DLPFC at 100% MT, in 40 2-second trains over 20 mins for 10 weekdays (total= 16,000 pulses).	**Outcomes measured:** HAMD, CGI-S, BDI. **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline and weekly thereafter for 2 weeks. **Type of Analysis:** NR

BDI Beck Depression Inventory; **CGI** Clinical Global Impression; **DLPFC** Dorsolateral Prefrontal Cortex; **DSM** Diagnostic and Statistical Manual; **ECT** Electroconvulsive Therapy; **HAMD** Hamilton Depression Rating Scale; **Hz** Hertz; **MT** Motor Threshold; **NR** Not reported; **rTMS** Repetitive Transcranial Magnetic Stimulation; **SD** Standard Deviation; **SSRI** Selective Serotonin Reuptake Inhibitor

5.3.5.2 Quality of Included Studies

Each of the fourteen RCTs comparing high and low frequency rTMS had areas where the risk of bias was low and unclear (**Table 10**). There were only three studies which were assessed as having a high risk of bias in one of the seven areas. All of the included studies used some type of randomization to allocate participants to either the high or low frequency rTMS arms. However, most of the included studies did not report the method of randomization so "random sequence generation" could not be assessed; these studies were therefore assessed as having "unclear" random sequence generation. Due to unclear methods of random sequence generation, it was also difficult to assess allocation concealment, and many received an "unclear" risk of bias in this area.

Similarly, blinding of personnel and participants was not clearly reported and most studies were assigned an "unclear" risk of participant and personnel blinding. All of the included studies except one used a blind outcome assessor; the remaining study was given a "high" risk of bias due to not having a blinded assessor.

All included studies had complete outcome data (making the risk of bias due to incomplete data outcome low), and showed no evidence of selective reporting, with the exception of Speer et al.[59] It is unknown whether other biases influenced the results of these studies. Due to this, "unclear risk of bias" was assigned to all included studies under the category "Other Bias."

Table 10: Quality Assessment of High Frequency rTMS versus Low Frequency rTMS Studies as Assessed by the Cochrane Risk of Bias[35]

Author	Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Any other bias?
Eche[99]	2012	Unclear	Unclear	High	Low	Low	Low	Unclear
Fitzgerald[63]	2003	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Fitzgerald[97]	2006a	Low	Unclear	Unclear	Low	Low	Low	Unclear
Fitzgerald[96]	2007	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Fitzgerald[95]	2009b	Low	Low	Unclear	Low	Low	Low	Unclear
Isenberg[94]	2005	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Miniussi[101]	2005	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Padberg[90]	1999	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Richieri[98]	2012	High	Unclear	Unclear	High	Low	Low	Unclear
Rossini[100]	2010	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Speer[59]	2009	Unclear	Unclear	Unclear	Low	Low	High	Unclear
Speer[60]	2013	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Stern[61]	2007	Unclear	Unclear	Low	Low	Low	Low	Unclear
Su[74]	2005	Unclear	Unclear	Unclear	Low	Low	Low	Unclear

5.3.5.3 Meta-analysis of Treatment Response

Eleven of the fourteen studies assessing high frequency versus low frequency rTMS provided adequate data on treatment response to permit pooling. **Figure 7** shows the response results (forest plot) for rTMS compared to sham. The definition of response as defined by each paper's authors was used in this analysis. Therefore, the scale and threshold for response varies by paper, as shown in the **Figure 7**. Four of these studies used the MADRS to define response, six used the HAMD and one used the BDI to determine response. Eight of the papers used a cut off of at least 50% reduction in depression score as the threshold for response. Of the remaining studies, one used 30% reduction, one used 20% reduction and one considered a final score under 15 on the MADRS as the definition of response.

The overall pooled risk ratio for high frequency versus low frequency rTMS is 1.19 (95% CI 0.97-1.46), favoring high frequency rTMS. This pooled estimate suggests that patients are more likely to experience treatment response with high frequency rTMS than with low frequency rTMS. However, as the 95% CI of this pooled estimate crosses the null line (1.00), this effect is not statistically significant. This result therefore

suggests that although there is a tendency for high frequency rTMS to result in more treatment responses, there is no statistically significant difference in response between high and low frequency rTMS.

The pooled studies were assessed for risk of publication bias using a Begg's funnel plot (**Figure 8**). This funnel plot is largely symmetrical, with points located equally along the x and y axes of the graph (p=0.161). This suggests that the risk of publication bias is low in this meta-analysis of treatment response.

Figure 7: Forest Plot of Response in Patients Receiving High Frequency rTMS versus those receiving Low Frequency rTMS Treatment

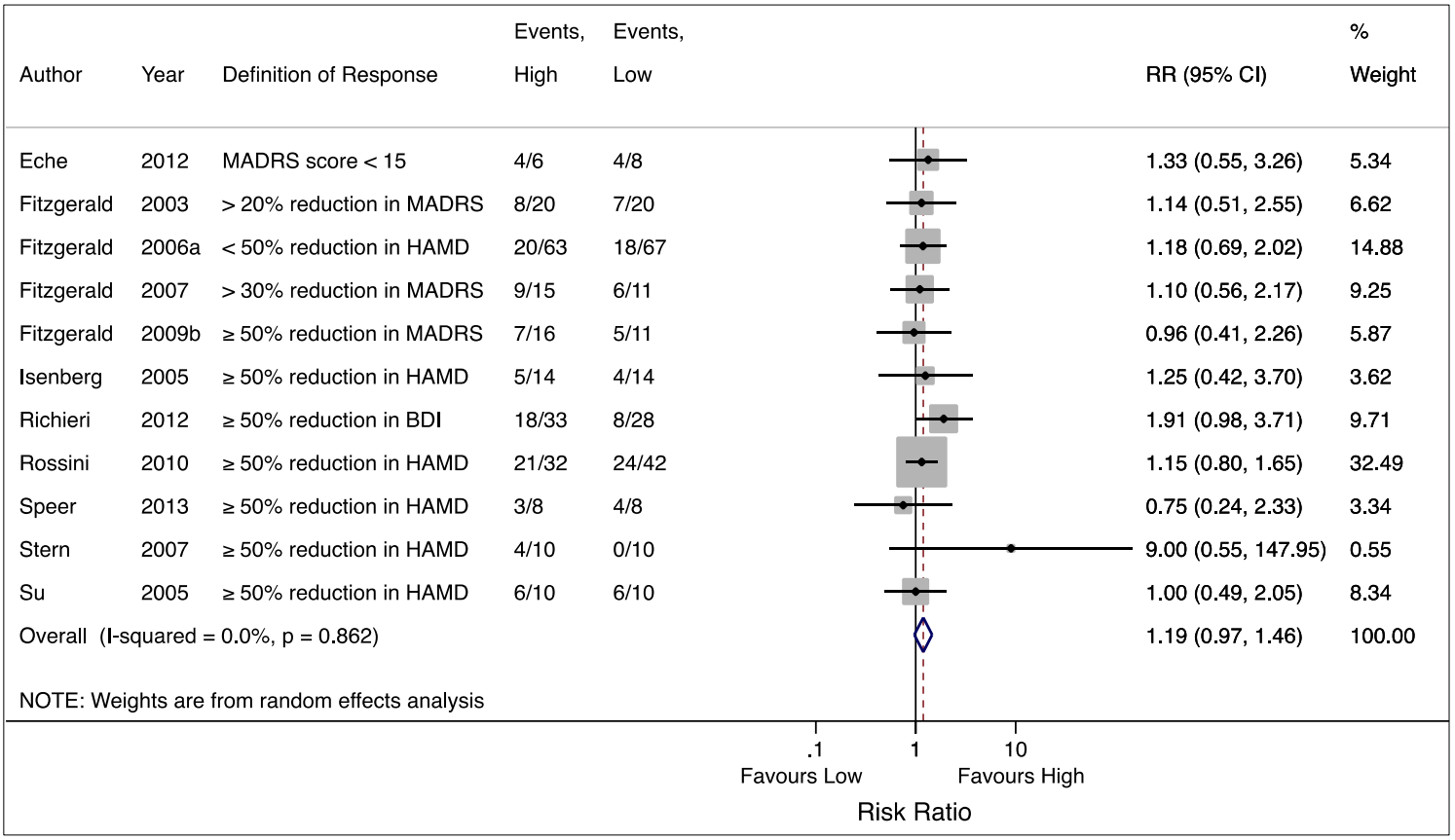
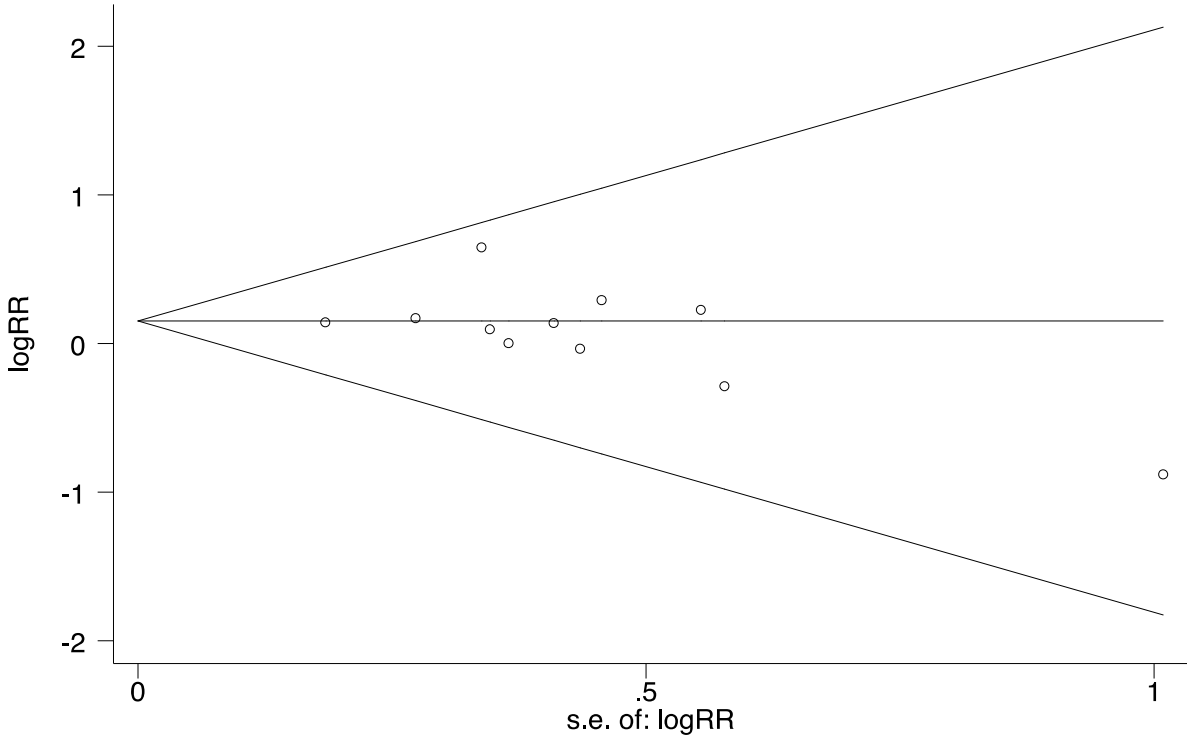


Figure 8: Beggs Funnel Plot with 95% Confidence Intervals to Test for Publication Bias in High Frequency rTMS versus Low Frequency rTMS (Response Outcome)



5.3.5.4 Meta-analysis of Remission

Six of the studies comparing high and low frequency rTMS provided adequate data on treatment remission to permit pooling. **Figure 9** shows the remission results (forest plot) for high and low frequency rTMS. The definition of remission as defined by each paper's authors was used in this analysis. Therefore, the scale remission varied by paper, as shown in the **Figure 9**. Five of the six papers pooled in this analysis defined remission using the HAMD. The remaining study used the MADRS to define remission[95]. The studies using the HAMD used cut off scores of 7[94], 8[74;97], 10[61] or 12[60] to define patient remission. The one study which used the MADRS defined remission as a score under 10[95].

The overall pooled risk ratio for high frequency rTMS versus low frequency rTMS remission rate is 1.29 with a 95% CI of 0.75-2.22. This pooled estimate suggests that patients are more likely to experience remission with high frequency rTMS than with low frequency rTMS. However, since the CI of this pooled estimate crosses the null line (1.00), this effect is not statistically significant. This evidence therefore suggests that although there is a tendency for treatment with high frequency rTMS to result in more remissions, there is no statistically significant difference in response between high and low frequency rTMS.

The pooled studies were assessed for risk of publication bias using a Begg's funnel plot (**Figure 10**). This funnel plot is largely symmetrical, with points located equally along the x and y axes of the graph (p=0.707). This suggests that the risk of publication bias is low in this meta-analysis of treatment response.

Figure 9: Forest Plot of Remission in Patients Receiving High Frequency rTMS versus those receiving Low Frequency rTMS Treatment

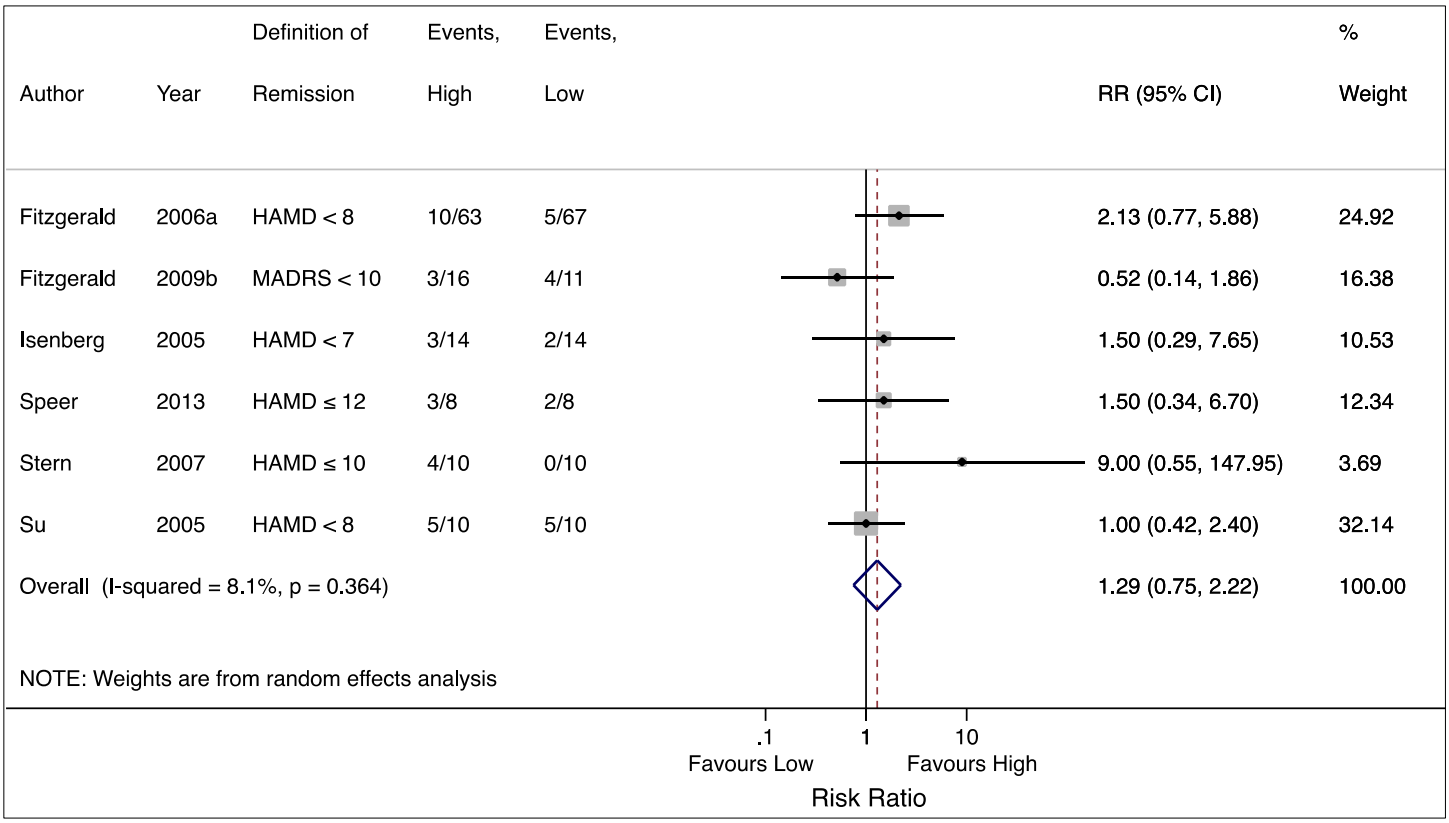
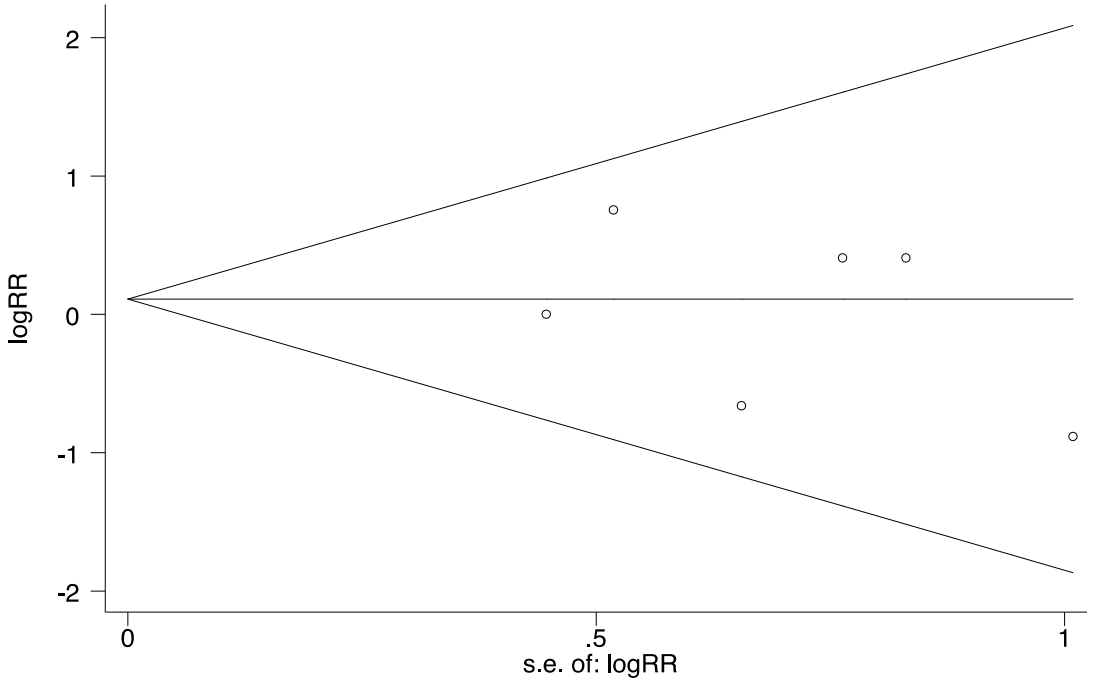


Figure 10: Beggs Funnel Plot with 95% Confidence Intervals to Test for Publication Bias in High Frequency rTMS versus Low Frequency rTMS (Remission Outcome)



5.3.5.5 Safety of High Frequency rTMS compared to Low Frequency rTMS

Of the included studies, only three reported adverse events, by group. Fitzgerald et al. reported that one participant in the high frequency group experienced a headache for longer than an hour, and that one participant in the high frequency group and one participant in the low frequency group experienced dizziness after treatment[63]. Su et al. reported that one participant in the high group and one in the low group experienced a headache[74]. Padberg et al. reported that three participants in the high frequency group and two in the low frequency group experienced pain[90]. They also reported that one participant in the high frequency group and one participant in the low frequency group experienced a headache[90]. There does not appear to be more minor adverse events with high or low frequency rTMS. No studies reported serious adverse events such as cognitive impairment or seizures.

5.3.5.6 Conclusions on High and Low Frequency Repetitive Transcranial Magnetic Stimulation

The optimal frequency of rTMS is unclear. There is a trend towards high frequency rTMS being more effective to achieve both clinical response and remission than low frequency. However, as these results are not statistically significant, high frequency may be less effective, equivalent or more effective compared to low

frequency. No serious safety concerns were assessed; mild side-effects reported include mild headaches, dizziness and discomfort/pain did not differ between frequency protocols.

5.3.6 Unilateral Repetitive Transcranial Magnetic Stimulation Compared to Bilateral Repetitive Transcranial Magnetic Stimulation

5.3.6.1 Characteristics of Included Studies

Five RCTs comparing the efficacy of unilateral and bilateral rTMS were included in this HTA[41;65;102-104]. Characteristics of each included study have been summarized in **Table 11**. Three studies were conducted in Australia[103-105], one was conducted in the United States[102] and one was conducted in Canada[41].The studies were published between 2010[102] and 2013[103]. One of the studies used a modified intention-to-treat analysis[41], and the remaining did not report what type of analysis was conducted.

The protocol used for rTMS varied amongst the included studies. For the bilateral rTMS arms, all of the included studies used a frequency of 1 hertz[41;65;102-104]; for the unilateral rTMS arms the studies used either 1[102-104] or 10[41;65] hertz. The motor threshold used in each study varied from 100% to 120%. The participants in these studies received between 10 and 20 sessions over a period of two to four weeks.

The definition of treatment resistant did not vary widely amongst the included studies. All of the included studies in this category reported their definition of treatment resistance, and all used a cut off of at least 2 adequate antidepressant trials[41;65;102-104].

Table 11: Characteristics of Studies Assessing the Efficacy of Unilateral rTMS versus Bilateral rTMS

Author, Year of Publication, Country	*Patient Selection*	*Comparators*	*Outcomes*
Blumberger[41] 2012, Canada	**Patient Selection:** Patient recruited from 3 outpatient clinics between January 2006 and January 2009 and were randomized using a computer-generated list. **Inclusion Criteria:** Age 18-85, DSM-IV diagnosis of MDD without psychotic features based on the Structured Clinical Interview for DSM-IV, score of greater than 21on HAMD-17, receiving stable doses of psychotropic medications for at least four weeks prior to randomization, capable to consent as assessed based on their ability to provide a spontaneous narrative description of the key elements of the study using the MacArthur Competence Assessment Tool for Clinical Research, currently an outpatient. **Exclusion Criteria:** DSM-IV substance dependence in the last 6 months (excluding nicotine) or DSM-IV substance abuse in the last month, met DSM-IV criteria for borderline personality disorder or antisocial personality disorder based on the Structured Clinical Interview for DSM-IV Axis II Disorders, Bipolar I, II or NOS, had a significant unstable medical or neurologic illness or a history of seizures, acutely suicidal, pregnant, metal implants in the cranium, had a known diagnosis of dementia or a current MMSE score less than 26, had received benzodiazepines (dose equivalent > lorazepam 2 mg/day), monoamine oxidase inhibitors, or buproprion during the previous four weeks, received prior treatment with rTMS for any indication. **Patient Characteristics:** Twenty-six patients with a mean age of 58.0 (12.5), 14 females and12 males were randomized to unilateral rTMS. Twenty-two patients with a mean age of 48.9 (13.4), 12 females and 10 males were randomized to Bilateral rTMS. **Definition of Treatment Resistance:** Failed to achieve a clinical response, or did not tolerate, at least two separate trials of antidepressants from different classes at sufficient dose for at least 6 weeks according to Stage II criteria outline by Thase and Rush (1995).	**Unilateral:** 10 Hz rTMS to left DLPFC at 100% MT for 29 trains of 50 pulses (1450 total treatment) 5 days per week for 3 weeks. **Bilateral:** 1 Hz rTMS to right DLPFC at 100% MT for 4+1 trains of 65 pulses (465 pulses total treatment), then 10 Hz rTMS to left DLPFC at 100% MT for 15 trains of 50 pulses (750 total treatment) 5 days per week for 3 weeks.	**Outcomes measured:** HAM-D, RBANS, HVLTR, BVMT-R, Grooved Peg Board test. **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline and every 5 treatments. **Type of Analysis:** Modified Intention to Treat
Fitzgerald[104] 2011, Australia	**Patient Selection:** Patients were recruited from inpatients of 4 hospitals between January 2006 and May 2009 and were randomized using computer generation. **Inclusion Criteria:** HAMD-17 score > 13 **Exclusion Criteria:** Significant currently active medical illness, current neurological disease, contraindication to rTMS, a current DSM-IV diagnosis of alcohol or substance dependence, other concurrent axis 1 psychiatric disorders. **Patient Characteristics:** Seventy-one patients with a mean age of 47.9 (14.1), 47 females and 24 males were randomized to unilateral right low frequency rTMS. Seventy-one patients with a mean age of 45.7 (13.7), 52 females and 19 males were randomized to bilateral right low frequency, left high frequency rTMS. Seventy-six patients with a mean age of 47.9 (13.7), 48 females and 28 males were randomized to bilateral right low frequency, left low frequency rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode.	**Unilateral:** 1 Hz rTMS to the right PFC at 110% MT for 1 train (900 pulses), 5 days per week for 2 weeks. **Bilateral low/high:** 1 Hz rTMS to the right hemisphere at 110% MT for 1 train (900 pulses); 10 Hz rTMS to the left hemisphere at 110% MT for 18 trains (900 pulses), 5 days per week for 2 weeks. **Bilateral low/low:** 1 Hz rTMS to the right hemisphere at 110% MT for 1 train (900 pulses); 1 Hz to the left hemisphere at 110% MT for 1 train (900 pulses), 5 days per week for 2 weeks.	**Outcomes measured:** HAMD, BDI, BAI **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks, and 4 weeks. **Type of Analysis:** NR

Fitzgerald[65] 2012, Australia	**Patient Selection:** Patients were recruited from a single site between January 2008 and November 2010 and were randomized (method not specified). **Inclusion Criteria:** HAMD-17 score > 15 **Exclusion Criteria:** Bipolar disorder**,** significant currently active medical illness, current neurological disease, contraindication to rTMS. **Patient Characteristics:** Twenty-four patients with a mean age of 43.4 (12.7.1), 15 females and 9 males were randomized to unilateral left high frequency rTMS. Twenty-two patients with a mean age of 40.5 (15.5), 14 females and 8 males were randomized to bilateral right low frequency, left high frequency rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode.	**Unilateral left:** 10 Hz rTMS to the left hemisphere at 120% MT for 30 trains for 3 weeks. **Bilateral:** 1 Hz rTMS to the right hemisphere at 120% MT for 1 train; 10 Hz to the left hemisphere at 120% MT for 30 trains for 3 weeks.	**Outcomes measured:** HAMD, MADRS BDI, CORE, STAI, DPDI, Wechsler Test of Adult Reading, Rey Auditory Verbal Learning Test, Brief Visual Spatial Memory Test, Digit Span, Trail Making Test A & B, Stroop and COWAT phonemic Fluency. **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline, 3 weeks, and 6 weeks. **Type of Analysis:** NR
Fitzgerald[103] 2013, Australia	**Patient Selection:** Patients were recruited from inpatients at 4 hospitals between February 2009 and October 2010 and were randomized using computer generation. **Inclusion Criteria:** HAMD-17 score > 13 **Exclusion Criteria:** Current and significant active medical illness, current neurological disease or a contraindication to rTMS (e.g. history of a seizure disorder; the presence of a pacemaker or metal somewhere in the head other than the teeth). **Patient Characteristics:** Ninety-one patients with a mean age of 46.7 (14.2), 59 females and 32 males were randomized to unilateral right low frequency rTMS. Eighty-eight patients with a mean age of 48.5 (15.9), 66 females and 22 males were randomized to bilateral right low frequency, left high frequency rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode.	**Unilateral:** 1 Hz rTMS to right side at 110% MT for 1 train (900 pulses) 5 days per week for 4 weeks. **Bilateral:** 1 Hz rTMS to right side at 110% MT for 1 train (900 pulses) followed by left-sided 10 Hz at 110% MT for 15 trains of 50 pulses 5 days per week for 4 weeks.	**Outcomes measured:** HAMD, BDI, BAI **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks, 4 weeks. **Type of Analysis:** NR
Pallanti[102] 2010, United States	**Patient Selection:** Participants were recruited from 1 hospital between March 2009 and October 2009 and were randomized (method not reported). **Inclusion Criteria:** HAMD score ≥18 **Exclusion Criteria:** Any additional psychiatric comorbidity, as assessed by the Structured Clinical Interview for Diagnosis; rTMS contraindications such as metallic implants, foreign bodies or history of seizures; substance abuse in the previous 6 months; any major medical disease; and inability or refusal to provide written informed consent. **Patient Characteristics:** Twenty patients with a mean age of 51.2 (2.53), 12 females and 8 males were randomized to the unilateral low frequency rTMS. Twenty patients with a mean age of 47.6 (12.33), 11 females and 9 males were randomized to the bilateral right low frequency rTMS, left high frequency rTMS.. **Definition of Treatment Resistance:** At least two previous failed antidepressant trials, each lasting at least 6 weeks.	**Unilateral:** 1 Hz rTMS to the right DLPFC at 110% of MT for 3 140-second trains, followed by a 30s intertrain interval (a total of 420 stimuli per session). Ffteen daily sessions were administered only on weekdays, beginning on Monday. **Bilateral:** 1 Hz rTMS to the right DLPFC at 110% MT for 3 140-s trains, followed by a 30s intertrain interval (a total of 420 stimuli per session), followed by 10 Hz rTMS to the left DLPFC at 100% MT,for 20 5-second trains and a 25-s intertrain interval (a total of 1000 stimuli per session were applied over the left DLPFC). Fifteen daily sessions were administered only on weekdays, beginning on Monday.	**Outcomes measured:** HAMD **Follow-up time:** 3 weeks **Outcome ascertainment:** Baseline, 1 week, 2 weeks, and 3 weeks. **Type of Analysis:** NR

BDI Beck Depression Inventory; **CGI** Clinical Global Impression; **DLPFC** Dorsolateral Prefrontal Cortex; **DSM** Diagnostic and Statistical Manual; **ECT** Electroconvulsive Therapy; **HAMD** Hamilton Depression Rating Scale; **Hz** Hertz; **MADRES** Montgomery-Asberg Depression Rating Scale**; MT** Motor Threshold; **NR** Not reported; **rTMS** Repetitive Transcranial Magnetic Stimulation; **SD** Standard Deviation; **SSRI** Selective Serotonin Reuptake Inhibitor

5.3.6.2 Quality of Included Studies

All of the five RCTs comparing unilateral and bilateral rTMS had areas where the risk of bias was low and unclear (**Table 12**). None of the studies were assessed as having "high" risk of bias areas. All of the included studies used some type of randomization to allocate participants to either the unilateral or bilateral rTMS arms. Four of the included studies reported their method of allocating participants, and based on these methods, were determined to be at "low" risk of bias for randomization[41;102-104]. One study did not report their method of random sequence generation and therefore received an "unclear" risk of bias for this area[65]. Four out of five included studies did not report information on allocation concealment, and therefore received "unclear" risk of bias for this category[41;65;103;104].

The included studies all had "unclear" risk of bias for blinding of participants and personnel. However, all of the included studies reported that a blind assessor was used to measure study outcomes, and all five studies were given a "low" risk of bias for this area.

All included studies had complete outcome data (making the risk of bias due to incomplete data outcome low), and showed no evidence of selective reporting. It is unknown whether other biases influenced the results of these studies. Due to this, "unclear risk of bias" was assigned to all included studies under the category "Other Bias."

Table 12: Quality Assessment of Unilateral rTMS versus Bilateral rTMS Studies as Assessed by the Cochrane Risk of Bias[35]

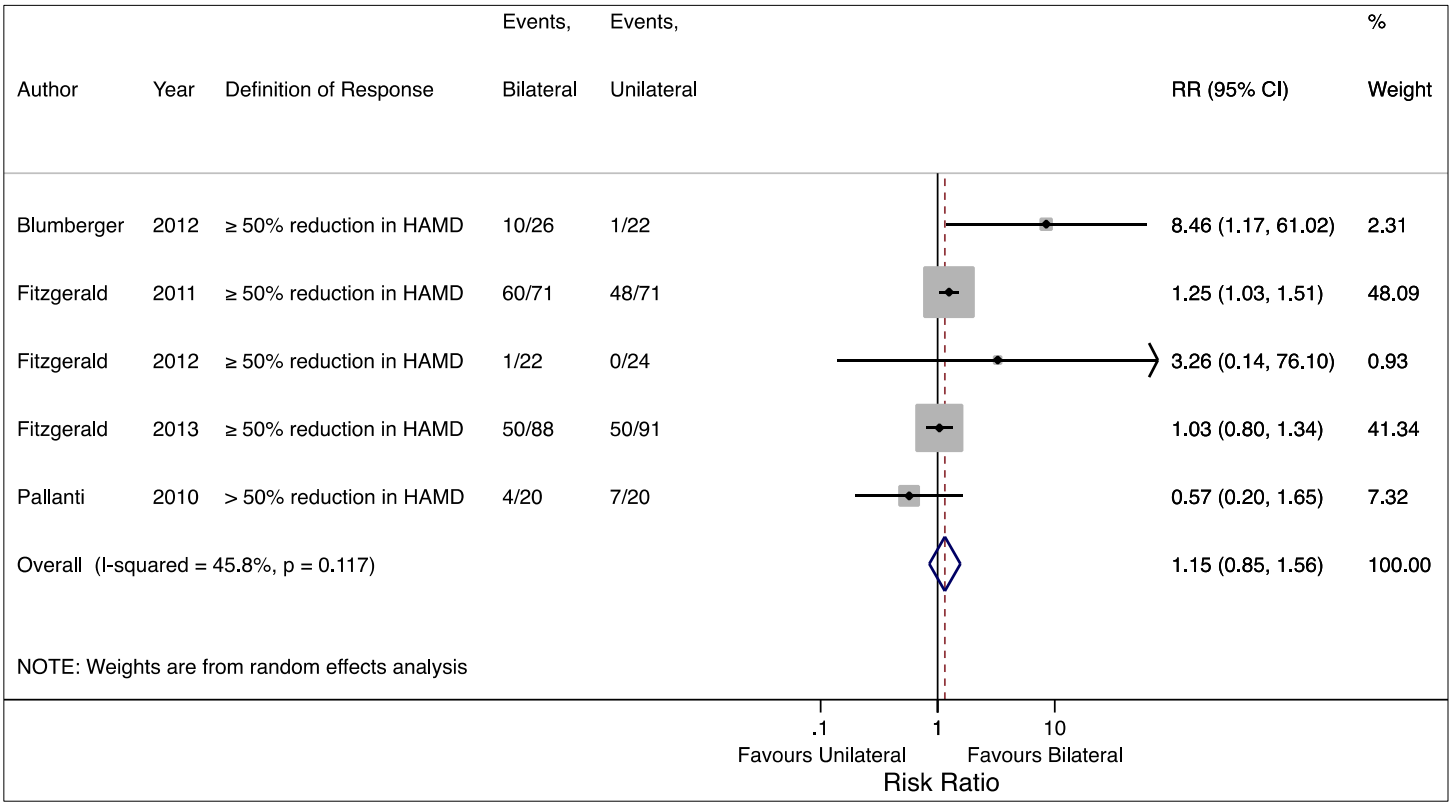
Author	Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Any other bias?
Blumberger[41]	2012	Low	Unclear	Unclear	Low	Low	Low	Unclear
Fitzgerald[104]	2011	Low	Unclear	Unclear	Low	Low	Low	Unclear
Fitzgerald[65]	2012	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Fitzgerald[103]	2013	Low	Unclear	Unclear	Low	Low	Low	Unclear
Pallanti[102]	2010	Low	Low	Unclear	Low	Low	Low	Unclear

5.3.6.3 Meta-analysis of Treatment Response

Five of the studies comparing unilateral and bilateral rTMS provided adequate data on treatment response to permit pooling[41;65;102-104]. **Figure 11** shows the response results (forest plot) for rTMS compared to sham. In this analysis, all studies used the HAMD with a 50% score reduction cut off to define response[41;65;102-104].

The overall pooled risk ratio for unilateral versus bilateral rTMS is 1.15 (95% CI: 0.85-1.56), favoring bilateral rTMS. This pooled estimate suggests that patients are more likely to experience treatment response with bilateral rTMS than with unilateral rTMS. However, as the 95% CI of this pooled estimate crosses the null line (1.00), this effect is not statistically significant. This result therefore suggests that although there is a tendency for bilateral rTMS to result in more treatment responses, there is no statistically significant difference in response between bilateral and unilateral rTMS.

Figure 11: Forest Plot of Response in Patients Receiving Unilateral rTMS versus those receiving Bilateral rTMS Treatment

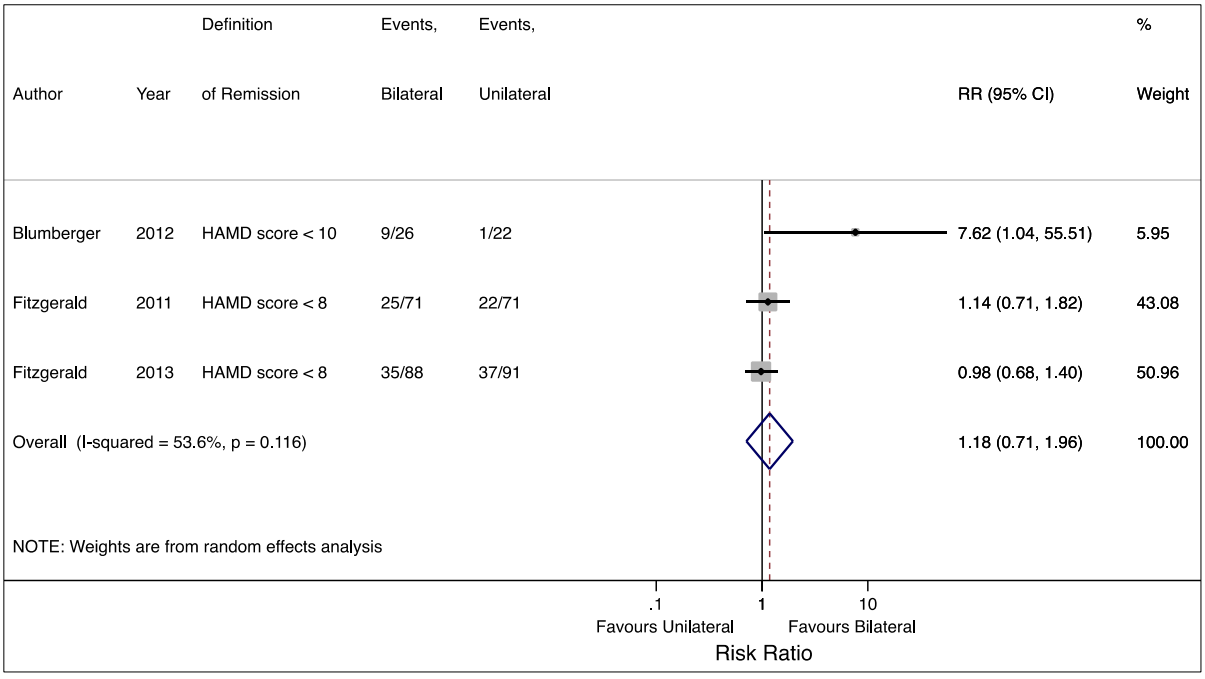


5.3.6.4 Meta-analysis of Remission

Only three of the studies comparing unilateral and bilateral rTMS provided adequate data on treatment remission to permit pooling. **Figure 12** shows the remission results (forest plot) for high and low frequency rTMS. The definition of remission as defined by each paper's authors was used in this analysis. Therefore, the scale used to measure remission varied by paper, as shown in the **Figure 12**. All three of the papers used the HAMD. Two of the papers used a cut off score of 8[103;104], and the other paper used a cut off score of 10[41].

The overall pooled risk ratio for unilateral rTMS versus bilateral rTMS remission rate is 1.18 with a 95% CI of 0.71-1.96, favoring bilateral rTMS. This pooled estimate suggests that patients are more likely to experience remission with bilateral rTMS than with unilateral rTMS. However, since the CI of this pooled estimate crosses the null line (1.00), this effect is not statistically significant. This evidence therefore suggests that although there is a tendency for treatment with bilateral rTMS to result in more cases of remission, there is no statistically significant difference in remission rates between bilateral and unilateral rTMS.

Figure 12: Forest Plot of Remission in Patients Receiving Unilateral rTMS versus those receiving Bilateral rTMS Treatment



5.3.6.5 Safety of Unilateral Repetitive Transcranial Magnetic Stimulation compared to Bilateral Repetitive Transcranial Magnetic Stimulation

Of the five included studies, three reported side effects due to treatment. Blumberger et al. reported that one patient in the unilateral group experienced headache pain, and one experienced scalp pain; no patients from the bilateral group reported any adverse events[41]. Pallanti et al. reported eight adverse events: in the unilateral group one participant had a headache and two participants reported cognitive complaints, in the bilateral group one participant had a headache, one patient complained of scalp pain, and three participants reported cognitive complaints in the bilateral group[102]. Fitzgerald et al. reported four adverse events: in the right-side unilateral group one participant reported having a headache and one participant reported increased agitation, in the bilateral low frequency group one participant reported discomfort and one participant reported a worsening of their pre-existing migraine condition[104]. No major adverse events were assessed in any of the studies.

5.3.6.6 Conclusions on Bilateral and Unilateral Repetitive Transcranial Magnetic Stimulation

The optimal location of treatment for rTMS is unclear. There is a trend towards bilateral rTMS being more effective to achieve both clinical response and remission than bilateral. However, both 95% CIs cross 1.0 indicating that compared to bilateral, unilateral rTMS may be equivalent, more effective or less effective. No serious safety concerns were identified; the side effects reported include headaches, agitation, and discomfort/pain and appear to be equivalent for both treatment locations.

5.3.7 High Intensity Repetitive Transcranial Magnetic Stimulation Compared to Low Intensity Repetitive Transcranial Magnetic Stimulation

5.3.7.1 Characteristics of Included Studies

Three RCTs comparing high intensity rTMS with low intensity rTMS were included in this HTA[76;78;79]. Characteristics of each included study have been summarized in **Table 13**. Each study was conducted in a different country: one in Turkey[79], one in Germany[76] and one in Italy[78]. The studies were published between 2002[76] and 2012[79]. Each study included between 20[76] and 36[78] participants, with a total of 79 participants included in all three studies[76;78;79].

The protocol used for rTMS varied amongst the included studies. Frequencies of 10[76], 15[78] and 20[79] hertz were used in these studies. For the low intensity arms, motor thresholds of 80%[78;79] or 90%[76] were used, while in the

high intensity arms, motor thresholds of 100%[76;78] or 110%[79] were used. The number of rTMS sessions provided to each participant varied from 10[76;78] to 30[79], over a period of 2[76;78] to 6 weeks[79].

The definition of treatment resistant did not vary amongst the included studies. All of the included studies in this category reported their definition of treatment resistance, and all used a cut off of at least 2 adequate antidepressant trials[76;78;79].

Table 13: Characteristics of Studies Assessing the Efficacy of High Intensity rTMS versus Low Intensity rTMS

Author, Year of Publication, Country	*Patient Selection*	*Comparators*	*Outcomes*
Bakim[79] 2012, Turkey	**Patient Selection:** Patient were recruited from 1 psychiatric outpatient clinic (recruitment dates not reported) and were randomized by computer program. **Inclusion Criteria:** Age 18-65, a diagnosis of unipolar major depression, recurrent or single episode and without psychotic features, right-handed, HAMD-17 score ≥ 18 or MADRS score ≥ 20. **Exclusion Criteria:** Comorbidity of any other Axis I disorder, including alcohol and substance use disorders, current or past history of epilepsy, head trauma, encephalitis, meningitis, or any other cerebrovascular disease, pregnancy, any pace-maker or medical pumps replaced in the body or a metal implant in the skull, any use of ECT, antipsychotics or anticonvulsants which may interfere with the excitability of cortical neurons and change the MT, inability to read and understand the Turkish language. **Patient Characteristics:** Twelve participants with a mean age of 38.8 (9.9), 10 females and 2 males were randomized to low intensity rTMS. Eleven participants with a mean age of 43.1 (8.2), 10 females and 1 male were randomized to high intensity rTMS. **Definition of Treatment Resistance:** No response to adequate courses (at least 6 weeks) of at least two different classes of antidepressants used at optimal doses.	**Low:** 20 Hz rTMS to left DLPFC at 80% MT for 20 trains of 40 pulses (24000 total treatment) once per day for 6 weeks. **High:** 20 Hz rTMS to left DLPFC at 110% MT for 20 trains of 40 pulses (24000 total treatment) once per day for 6 weeks.	**Outcomes measured:** HAMD, MADRS **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline and every week for 6 weeks. **Type of Analysis:** NR
Padberg[76] 2002, Germany	**Patient Selection:** Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** Organic brain disorders, pacemakers, mobile metal implants or implanted medication pumps. **Patient Characteristics:** Ten patients with a mean age of 60.3 (4.1), 7 women and 3 men were randomized to low-intensity rTMS. Ten patients with a mean age of 62.1 (4.6), 6 women and 4 men were randomized to high intensity rTMS,. **Definition of Treatment Resistance:** At least two antidepressant trials of adequate duration and dosage without significant clinical improvement.	**Low:** 10 Hz rTMS to left DLPFC at 90% intensity MT, for 1500 stimuli/day, 10 s, 15 trains, 30 s intertrain-interval). Patients underwent 10 afternoon sessions of within two weeks. **High-intensity:** 10 Hz rTMS to left DLPFC at 100% MT, for 1500 stimuli/day, 10 s, 15 trains, 30 s intertrain-interval). Patients underwent 10 afternoon sessions of within two weeks.	**Outcomes measured:** HAMD, MADRS, CGI, VAS and brief questionnaires to document side effects, tolerability, and rTMS-induced sensations. **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, 1 week and 2 weeks. **Type of Analysis:** NR
Rossini[78] 2005, Italy	**Patient Selection:** Patients were recruited from 1 hospital (recruitment dates not reported) and were randomized according to a computer-generated list. **Inclusion Criteria:** NR **Exclusion Criteria:** Age younger than 18 years and older than 75 years, history of seizures or neurological illnesses, severe medical conditions that could interfere with the clinical evaluation, pregnancy, mental retardation, and Edinburgh Handedness Inventory score below +70, and patients bearing pacemakers, mobile metal implants, implanted medical pumps or metal clips placed inside the skull. **Patient Characteristics:** Eighteen patients with a mean age of 54.0 (11.2), 15 females and 4 males were randomized to low intensity rTMS,. Eighteen patients with a mean age of 57.4 (8.7), 12 females and 6 males were randomized to the high-intensity rTMS group.. **Definition of Treatment Resistance:** A lack of improvement to at least two different treatments with antidepressants, at adequate dosage and duration, administered during the current episode.	**Low:** 15 Hz rTMS at 80% of MT, 2s train of stimulation. The inter-train interval was 28 s, and every subject received 20 trains of pulses per session. Patients underwent 10 sessions of stimulation over a 2-week period (Monday to Friday). **High-intensity:** 15 Hz rTMS at 100% of MT, 2 s train of stimulations. The inter-train interval was 28 s, and every subject received 20 trains of pulses per session. Patients underwent 10 sessions of stimulation over a 2-week period (Monday to Friday).	**Outcomes measured:** HAMD, CGI-S, and CGI-I. **Follow-up time:** 5 weeks **Outcome ascertainment:** Baseline (with the exception of CGI-I) and weekly for 5 weeks. **Type of Analysis:** NR

BDI Beck Depression Inventory; **CGI** Clinical Global Impression; **DLPFC** Dorsolateral Prefrontal Cortex; **DSM** Diagnostic and Statistical Manual; **ECT** Electroconvulsive Therapy; **HAMD** Hamilton Depression Rating Scale; **Hz** Hertz; **MADRES** Montgomery-Asberg Depression Rating Scale**; MT** Motor Threshold; **NR** Not reported; **rTMS** Repetitive Transcranial Magnetic Stimulation

5.3.7.2 Quality of Included Studies

All three of the RCTs comparing high and low intensity rTMS had areas where the risk of bias was low and unclear (**Table 14**). Only one of the studies had a "high" risk of bias in one of the seven areas[79]. All of the included studies used some type of randomization to allocate participants to either the high or low intensity rTMS arms. Two of the studies reported their method of randomization and it was deemed to be a "low" risk approach[78;79]. One study, Padberg et al. did not report their method of randomization and were therefore given an "unclear" risk of bias[76]. The risk of bias introduced by allocation concealment was unclear in all three studies[76;78;79].

The included studies all had "unclear" risk of bias for blinding of participants and personnel. However, all of the included studies reported that a blind assessor was used to measure study outcomes, and all five studies were given a "low" risk of bias for this area.

All included studies had complete outcome data (making the risk of bias due to incomplete data outcome low), and showed no evidence of selective reporting, with the exception of Bakim et al.[79]. It is unknown whether other biases influenced the results of these studies. Due to this, "unclear risk of bias" was assigned to all included studies under the category "Other Bias."

Table 14: Quality Assessment of High Intensity rTMS versus Low Intensity rTMS Studies as Assessed by the Cochrane Risk of Bias[35]

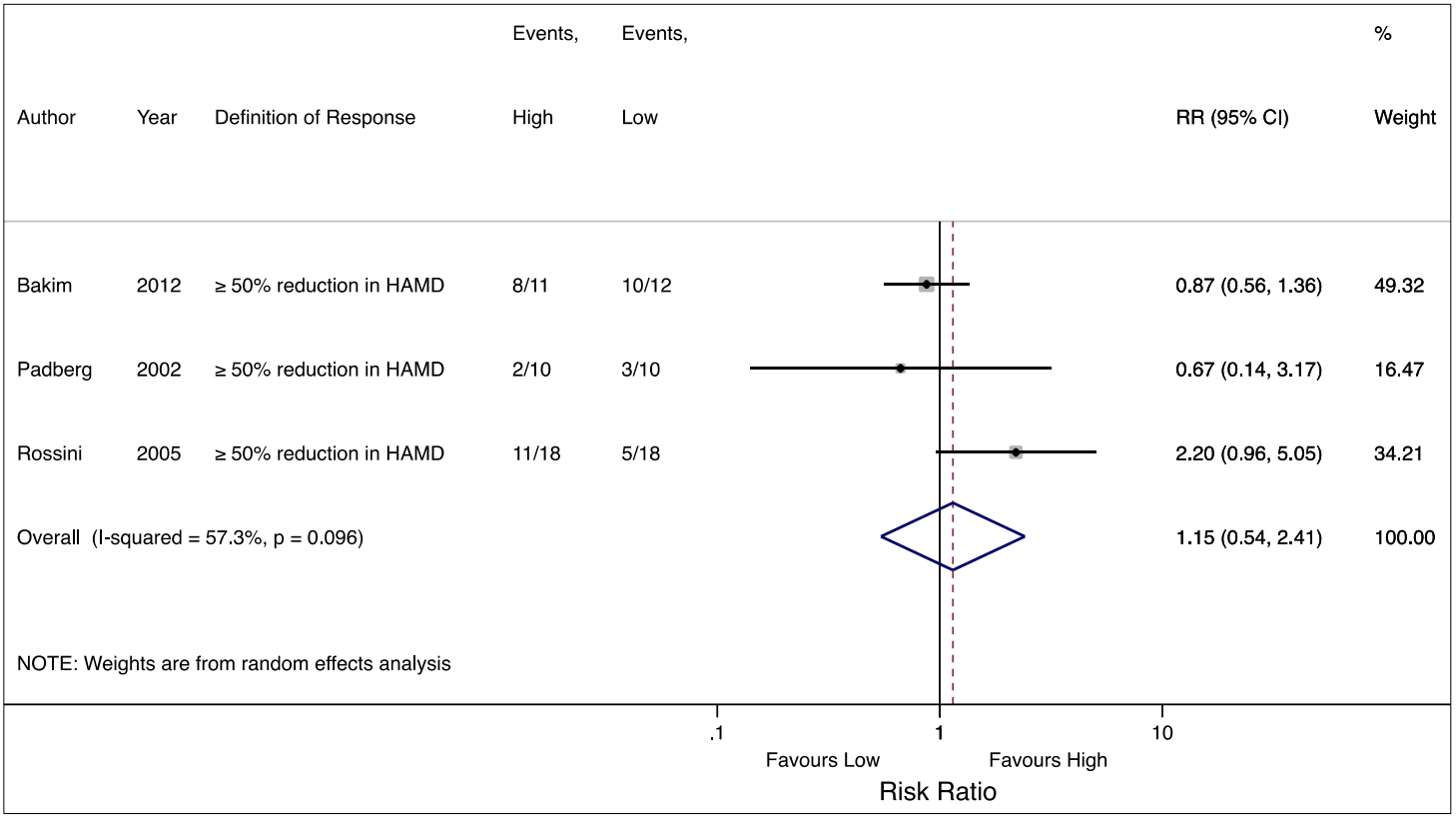
Author	Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Any other bias?
Bakim[79]	2012	Low	Unclear	Unclear	Low	Low	High	Unclear
Padberg[76]	2002	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Rossini[78]	2005	Low	Unclear	Unclear	Low	Low	Low	Unclear

5.3.7.3 Meta-analysis of Treatment Response

All three of the studies comparing high and low intensity rTMS provided adequate data on treatment response to permit pooling[76;78;79]. **Figure 13** shows the response results (forest plot) for rTMS compared to sham. All studies used the HAMD with a 50% score reduction cut off to define response[76;78;79].

The overall pooled risk ratio for high intensity versus low intensity rTMS is 1.15 (95% CI: 0.54-2.41), favoring high intensity rTMS. This pooled estimate suggests that patients are more likely to experience treatment response with high intensity rTMS than with low intensity rTMS. However, as the 95% CI of this pooled estimate crosses the null line (1.00), this effect is not statistically significant. This result therefore suggests that although there is a tendency for high intensity rTMS to result in more treatment responses, there is no statistically significant difference in response between high and low intensity rTMS.

Figure 13: Forest Plot of Response in Patients Receiving High Intensity rTMS versus those receiving Low Intensity rTMS Treatment



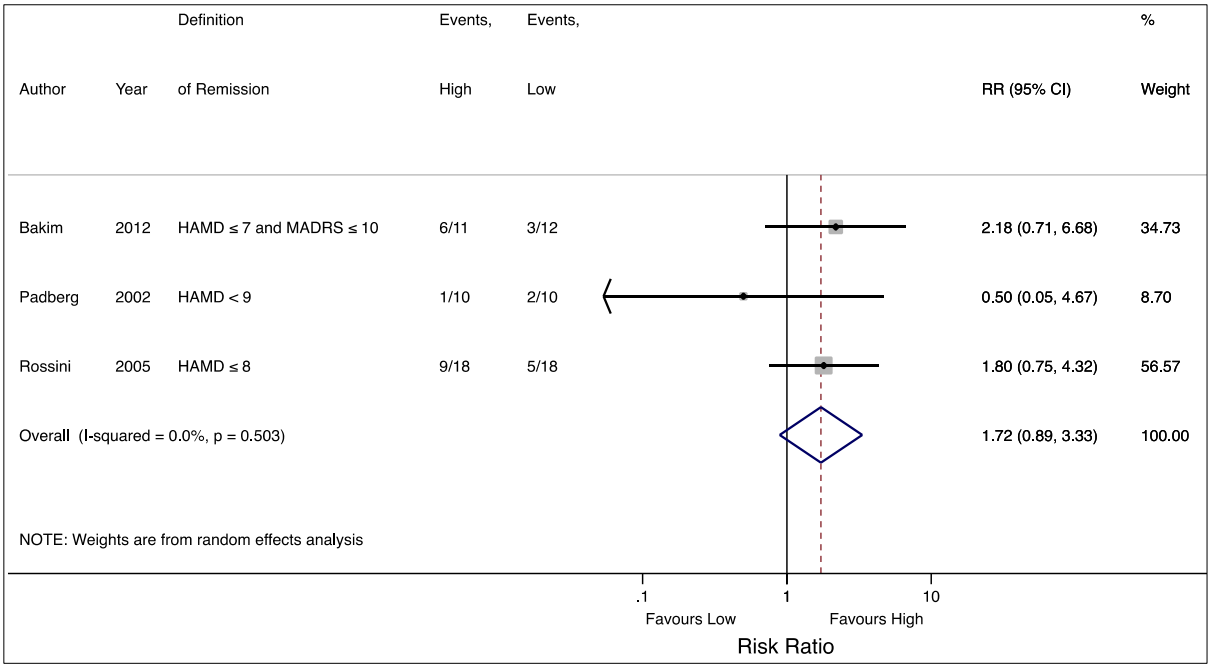
5.3.7.4 Meta-analysis of Remission

All three of the studies comparing high and low intensity rTMS provided adequate data on remission to permit pooling[76;78;79]. **Figure 14** shows the remission results (forest plot) for high and low intensity rTMS. All three

papers used the HAMD to assess remission: one used a cut off of 7[79], one used a cut off of [78]8 and one used a cut off of 9[76].

The overall pooled risk ratio for high versus low intensity rTMS remission rate is 1.72 (favoring high intensity) with a wide 95% CI of 0.89-3.33. This pooled estimate suggests that patients are more likely to experience remission with high intensity rTMS than with low intensity rTMS. However, since the CI of this pooled estimate crosses the null line (1.00), this effect is not statistically significant. This evidence therefore suggests that although there is a tendency for treatment with high intensity rTMS to result in more cases of remission, there is no statistically significant difference in response between high and low intensity rTMS.

Figure 14: Forest Plot of Remission in Patients Receiving High Intensity rTMS versus those receiving Low Intensity rTMS Treatment



5.3.7.5 Safety of high intensity repetitive transcranial magnetic stimulation compared to low intensity repetitive transcranial magnetic stimulation

All three of the included studies reported on adverse events. Padberg et al. reported that two patients experienced a tactical artifact and two experienced discomfort in the 100% motor threshold group, whereas

three patients experienced a tactical artifact and three experienced discomfort in the 90% motor threshold group [76]. Bakim et al. reported two participants in the 80% motor threshold group and 2 in the 100% motor threshold group experienced mild headaches[79]. Rossini et al. reported that two participants experienced a mild headache in the 80% motor threshold group. Two participants reported a mild headache and three reported discomfort at the site of treatment in the 100% motor threshold group [78]. Major adverse events were not assessed.

5.3.7.6 Conclusions on High and Low Intensity Repetitive Transcranial Magnetic Stimulation

The optimal intensity of rTMS is unclear. There is a trend towards high intensity rTMS being more effective to achieve both clinical response and remission than low intensity. However, as these results are not statistically significant, high intensity may be less effective, equivalent or more effective compared to low frequency. No serious safety concerns were identified; the minor side effects reported include headaches, tactile artifact during treatment, and discomfort/pain, and are equally distributed between both intensities.

5.3.8 Repetitive Transcranial Magnetic Stimulation Compared to Various other Repetitive Transcranial Magnetic Stimulation Protocols

5.3.8.1 Characteristics of Included Studies

Thirteen RCTs assessing rTMS compared to various other rTMS procedures were included[55;62;69;71;83;106-113]. Three of these investigated the use of image guidance in rTMS[69;83;106], two compared left and right cortex targeting[62;71], two compared the scheduling of rTMS sessions[110;111], one compared standard rTMS to rTMS using electroencephalogram activity[112], and five assessed the efficacy of combination protocols for rTMS treatment[55;107-109;113]. Characteristics of each included study have been summarized in **Table 15**. Six studies were conducted in Australia[106;108;110-113], two were conducted in Spain[69;71], two were conducted in the United States[55;62], and the remaining were conducted in Israel[109], Austria[107], and France[83]. The studies were published between 1996[71] and 2012[110]. Five studies used an intention-to-treat analysis[55;83;108;109;112], none reported using a per-protocol analysis, and the remaining did not report what type of analysis was conducted[62;69;71;106;107;110;111;113].

The rTMS protocols performed varied amongst the included studies. Frequency of rTMS used varied from 1[69] to 20[108;111;113] hertz (Hz), and motor threshold varied from 90%[71;83;108;112] to 120%[109]. Number of rTMS sessions provided to each participant varied from 5[107] to 20[109], over a period of 5 days[107] to 4 weeks[109].

The definition of treatment resistant also varied amongst the included studies. Of the included studies, three studies used a cut-off of at least one adequate trial of antidepressants[110;112;113], eight used a cut-off of at least 2 adequate antidepressant trials[62;69;83;106-109;111], and two used a cut-off of at least three adequate antidepressant trials[55;71].

Table 15: Characteristics of Studies Assessing the Efficacy of rTMS versus various other rTMS Protocols

Author, Year of Publication, Country	*Patient Selection*	*Comparators*	*Outcomes*
Image Guidance			
Fitzgerald[114] 2009a Australia	**Patient Selection:** Patients were recruited from 1 outpatient clinic and private psychiatrists between December 2005 and April 2007 and were randomized using computer generation. **Inclusion Criteria:** Age 18-70 years, major depressive disorder without psychosis, MADRS score > 20. **Exclusion Criteria:** Significant active medical illness, any history of epilepsy or other neurological illness, any contra-indication to MRI scanning. **Patient Characteristics:** Twenty-seven patients with a mean age of 43.9 (12.4), 18 females and 9 males were randomized to standard localization (5 cm method). Twenty-four patients with a mean age of 38.0 (12.2), 11 females and 13 males were randomized to targeted stimulation using neuro-navigation aided rTMS. **Definition of Treatment Resistance:** Failed at least 2 courses of antidepressants medications for at least 6 weeks in the current episode	**5 cm localization:** Patients underwent MRI then localization of the motor cortical site for optimal stimulation of a hand muscle and measurement 5 cm anteriorly along the scalp surface. 10 Hz rTMS AT 100% MT for 30 trains (1500 pulses per day, 30000 treatment total). **Neuro-navigation-aided localization:** Patients underwent MRI and stimulation sites in the DLPFC were identified based on task completion and gyral landmarks. 10 Hz rTMS AT 100% MT for 30 trains (1500 pulses per day, 30000 treatment total) .	**Outcomes measured:** MADRS, BDI, BPRS, CORE GAF, CGI, Hopkins verbal learning test, controlled oral word association test, Digit span, Brief visuospatial memory test-revised. **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 3 weeks, 4 weeks. **Type of Analysis:** NR
Garcia-Toro[69] 2006 Spain	**Patient Selection:** Patient recruitment method and dates not reported. Randomization was performed using sealed envelopes. **Inclusion Criteria:** Age > 18, unipolar major depression. **Exclusion Criteria:** High suicidal risk **Patient Characteristics:** Ten patients with a mean age of 48.5 (13.3), 4 females and 6 males received rTMS. Ten patients with a mean age of 51.1 (13.8), 4 females and 6 males received SPECT-guided rTMS. **Definition of Treatment Resistance:** Failed at least 2 trials of antidepressants medications	**rTMS:** Alternating 1 Hz at 110% MT for 30 trains with 20 Hz at 110% MT for 30 trains. **SPECT guided rTMS:** Alternating 1 Hz at 110% MT for 30 trains with 20 Hz at 110% MT for 30 trains with four regional responses guiding placement of the coil.	**Outcomes measured:** HAMD, GCI **Follow-up time:** 10 sessions (4 weeks) **Outcome ascertainment:** Baseline, 1 week, 2 weeks, 4 weeks **Type of Analysis:** NR
Paillère Martinot[83] 2010, France	**Patient Selection:** Patients were recruited 5 five teaching hospitals (recruitment dates not reported) and stratified randomization was performed in blocks using biostatistician-generated lists. **Inclusion Criteria:** NR **Exclusion Criteria:** Age > 65 years, alcohol or substance dependence in the past 6 months, ECT treatment in the past 6 months, any present medical condition, history of epileptic seizures, history of neurological disorders or substantial brain damage, and contraindication to magnetic fields. **Patient Characteristics:** Twenty patients with a mean age: 48.19 (7.77), 11 females and 9 males were randomized to standard rTMS. Sixteen patients with a mean age of 46.9 (7.26), 10 females and 6 males were randomized to the PET-guided group. **Definition of Treatment Resistance:** At least two trials of antidepressants of different classes given at adequate doses (>150 mg/d in an equivalent dose of imipramine) and duration (at least 4 wk for each drug).	**Standard:** rTMS target location was based on motor cortex location. 10 Hz rTMS at 90% of MT for 20 trains of 8 s with 60-s inter-train intervals resulting in a total of 1600 pulses over 20 min. rTMS was administered on 10 consecutive working days, providing a total of 16000 impulses. **PET-guided:** PET 3D-images were used to guide rTMS target location, either on the left or right hemisphere. 10 Hz rTMS at 90% of MT, 20 trains of 8 s with 60-s inter-train intervals resulting in a total of 1600 pulses over 20 min. rTMS was administered on 10 consecutive working days, providing a total of 16000 impulses.	**Outcomes measured:** MADRS, HAMD, and CGI-S. **Follow-up time:** 10 days **Outcome ascertainment:** Baseline and the last day of treatment (Day 10). **Type of Analysis:** Intention to treat
Right vs. Left Dorsolateral Prefrontal Cortex			

Pascual-Leone[71] 1996, Spain	**Patient Selection:** Patients were recruited from 1 hospital and 1 outpatient clinic (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** NR. **Exclusion Criteria:** NR **Patient Characteristics:** Seventeen patients with a mean age of 48.6 (SD not reported) entered into the multiple cross-over study (mean age, number of females and males were not reported by treatment group). **Definition of Treatment Resistance:** At least three episodes of depression that had been resistant to multiple medications, despite combinations and high dosage.	**Right-sided:** 10 Hz rTMS to right DLPFC at 90% of MT applied at different scalp positions. Five courses of rTMS were administered, each consisting of five sessions over 5 (consecutive) days. Each session consisted of 20 trains of 10 s duration separated by 1 min pauses. **Left-sided:** 10 Hz rTMS to left DLPFC at 90% of MT applied at different scalp positions. Five courses of rTMS were administered, each consisting of five sessions over 5 (consecutive) days. Each session consisted of 20 trains of 10 s duration separated by 1 min pauses.	**Outcomes measured:** HAMD and Beck's Questionnaire for patient self-rated mood. **Follow-up time:** 5 months **Outcome ascertainment:** Baseline and weekly throughout the study **Type of Analysis:** NR
Triggs[93] 2010, United States	**Patient Selection:** Participants were recruited from private psychiatrist practices, tertiary care center clinics, and the community by newspaper advertisements (recruitment dates not reported) and were randomized 1:1. **Inclusion Criteria:** NR **Exclusion Criteria:** A lifetime history of schizophrenia, schizoaffective disorder, other functional psychosis, rapid-cycling bipolar illness, alcohol or drug abuse within the past year; a positive urine drug test; axis II diagnosis of Cluster A (paranoid, schizoid, or schizotypal) or Cluster B (antisocial, borderline, histrionic, or narcissistic) personality disorder or mental retardation; use of medications that may lower seizure threshold (e.g. metronidazole) if the particular medication could not be stopped or altered without affecting the patient's medical care; history of neurological illness, epilepsy or seizure disorder, intracranial tumor, or major head trauma leading to loss of consciousness of any duration; evidence of central nervous system disease based on baseline complete neurological examination, EEG and contrast-enhanced computerized tomography or magnetic resonance imaging of the brain; history of implanted pacemaker or medication pump, metal plate in skull, or metal objects in the eye or skull; need for rapid clinical response due to conditions such as inanition, psychosis, or suicidality (defined as suicide attempt during the current major depressive episode or having a specific plan for committing suicide); a medical condition that was not well controlled, such as diabetes or hypertension, or concomitant medical or nutritional problems necessitating hospitalization; use of anticonvulsant mood stabilizers (e.g. carbamazepine, valproic acid); or inability to personally grant informed consent. **Patient Characteristics:** Sixteen patients with a mean age of 48.5 (10.8), 9 females and 7 males were randomized to right-sided rTMS group,. Eighteen patients with a mean age of 46.7 (15.3), 14 females and 4 males were randomized to left-sided rTMS. **Definition of Treatment Resistance:** Failed historically to respond to at least two separate trials (minimum duration 4 weeks) of therapeutic dosages of antidepressant medication (including at least one SSRI) or were intolerant of at least three different antidepressant medications (including at least one SSRI).	**Right-sided:** 5 Hz rTMS to right DLPFC at 100% of MT. Each daily treatment consisted of 2000 stimuli divided into 50 trains of 40 stimuli. Train duration was 8 s and inter-train interval was 22 s. Participants received 10 daily weekday sessions of either rTMS or sham rTMS over a 2-week period. **Left-sided:** 5 Hz rTMS to left DLPFC at 100% of MT. Each daily treatment consisted of 2000 stimuli divided into 50 trains of 40 stimuli. Participants received 10 daily weekday sessions of either rTMS or sham rTMS over a 2-week period.	**Outcomes measured:** HAMD, BDI, STAI. **Follow-up time:** 3 months **Outcome ascertainment:** Baseline (on 3 separate occasions during the 2-week period prior to rTMS), weekly during the 2-week rTMS treatment period, and 1 week, 1-month and 3-months following rTMS. **Type of Analysis:** NR
Scheduling			
Galletly[115] 2012 Australia	**Patient Selection:** Patients were recruited from private psychiatrists between August 2008 and Feb 2011 and were randomized using computer generation. **Inclusion Criteria:** Fluency in English, diagnosis of major depression. **Exclusion Criteria:** Neurological disorders, metal plates or other implants in the skull, a history of epilepsy, withdrawing from drugs or alcohol. **Patient Characteristics:** Thirty-five patients with a mean age of 45.6 (12.5), 24 females and 11 males were randomized to five days/week rTMS. Forty-two patients with a mean age of 51.0 (13.8), 27 females and 14 males were randomized to 3 days/week rTMS (spaced). **Definition of Treatment Resistance:** Failed at least 1 course of antidepressants medications in the current episode.	**Daily:** 10 Hz rTMS to left DLPFC at 110% of MT (1500 pulses) then 1 Hz to right DLPFC at 110% MT (900 pulses), 5 days per week for 4 weeks. **Spaced:** 10 Hz rTMS to left DLPFC at 110% of MT (1500 pulses) then 1 Hz to right DLPFC at 110% of MT (900 pulses), 3 days per week for 6 weeks.	**Outcomes measured:** HAMD, MADRS, Zung SDS, HARS. **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline, 4 weeks, 6 weeks. **Type of Analysis:** NR

Turnier-Shea[111] 2006, Australia	**Patient Selection:** Patients were recruited from 1 hospital and from private outpatient clinics (recruitment dates not reported) and were randomized by coin flip. **Inclusion Criteria:** Major depressive episode (DSM-IV), between 20 and 65 years, HAMD-17 score ≥ 18, and no medication change for a minimum of 2 weeks before commencement of the study. **Exclusion Criteria:** Concurrent neurological disorder (including epilepsy), other concurrent serious medical illness, history of significant head injury, recent alcohol or other drug misuse, and intracranial metal object. **Patient Characteristics:** Eight patients with a mean age of 40.5 (10.1), 4 females and 4 males years were randomized to daily rTMS, Eight patients with a mean age of 46.4 (10.7), 6 females and 2 males were randomized to spaced rTMS,. **Definition of Treatment Resistance:** Failure to respond to trials of at least two different antidepressants, at maximum manufacturer recommended doses, for at least 4 weeks.	**Daily:** 20 Hz rTMS to left DLPFC at 100% of MT, 30 2-second trains, with an inter-train interval of 28 seconds. rTMS was delivered on days 1–5 and 8–12 for a total of 10 treatments over 2 weeks. **Spaced:** 20 Hz rTMS to left DLPFC at 100% of MT, 30 2-second trains, with an inter-train interval of 28 seconds. rTMS was delivered on days 1, 3, 5, 8 and 12 for a total of five treatments over 2 weeks.	**Outcomes measured:** HAMD, VAS. **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, 1 week, and 2 weeks **Type of Analysis:** NR
Electroencephalography-timed			
Price[112] 2010, Australia	**Patient Selection:** Participants were recruited from outpatient clinics (recruitment dates not reported) and were randomized using predetermined lists. **Inclusion Criteria:** NR **Exclusion Criteria:** NR **Patient Characteristics:** Twenty-three patients with a mean age of 46.3 (13.0), 9 females and 14 males were randomized to standard rTMS group. Twenty-one patients with a mean age of 40.2 (12.9), 11 females and 10 males were randomized to interactive rTMS. **Definition of Treatment Resistance:** Failed at least one previous antidepressant treatment.	**Standard:** 10 Hz rTMS comprised of forty 5-second trains at 90-100% of MT with a 25-second inter-train interval. **Interactive:** 10 Hz rTMS where stimuli were applied in response to real-time analysis of the background EEG. The total of stimuli in each train was one more (17x3) than the standard technique with a 15-second inter-train interval.	**Outcomes measured:** HAMD, BDI. **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks, and 4 weeks. **Type of Analysis:** Intention to treat
Combination Protocols			
Conca[107] 2002 Austria	**Patient Selection:** Patients were recruited from inpatients from 1 hospital (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** NR **Exclusion Criteria:** NR **Patient Characteristics:** Twelve patients with mean age of 48.2 (16.1), 9 females and 3 males were randomized to high/low frequency rTMS on both right and left side. Twelve patients with a mean age of 44.8 (14.8), 8 females and 4 males were randomized to high/low frequency rTMS on left side only. Twelve patients with a mean age of 46.8 (10.3), 8 females and 4 males were randomized to high frequency on the left side only. **Definition of Treatment Resistance:** Failure to respond to two different adequate monotherapy trials of medications with different pharmacological profiles and the failure to response to a second augmentation strategy.	**High/Low 1:** 10 Hz rTMS to left DLPFC at 110% MT for 10 trains of 60 pulses and 1 HZ rTMS to right DLPC 110% MT for 1 train of 300 pulses (6500 total treatment) for 5 days. **High/Low 2:** 10 Hz rTMS to left DLPFC at 110% MT for 10 trains alternating with 1 Hz 30 train (6500 total treatment) for 5 days. **High**: 10 Hz rTMS to left DLPFC at 110% MT for 13 trains (6500 total treatment) for 5 days.	**Outcomes measured:** CGI **Follow-up time:** 5 days **Outcome ascertainment:** baseline and 5 days **Type of Analysis:** NR
Fitzgerald[108], 2008, Australia	**Patient Selection:** Participants were recruited from 1 outpatient clinic and by psychiatrist referral between September 2005 and January 2007 and were randomized using a single, computer-generated, random-number sequence. **Inclusion Criteria:** Age 18-70, diagnosis of major depressive episode or bipolar affective disorder, score of more than 20 on MADRS, ability to attend hospital daily for four weeks of treatment, treatment resistant. **Exclusion Criteria:** NR **Patient Characteristics:** Twenty-eight patients with a mean age of 44.8 (11.4), 13 female and 15 male were randomized to receive non-primed rTMS., Thirty participants with a mean age of 45.7 ± 10.8 years, 20 female and 10 male were randomized to receive primed rTMS,. **Definition of Treatment Resistance:** Failure to respond to at least 2 antidepressant medications for at least 6 weeks during the current episode.	**Non-primed:** A sham priming stimulation was first provided with the coil angled away from the scalp at 45 degrees from the side of the coil, with a 6 Hz stimulation for twenty trains of 5 seconds duration at 90% of the MT, applied with a 25-second intertrain interval. Then 1 Hz rTMS at 110% of MT for one continuous, 15-minute train. Patients received 10 sessions of treatment on a daily basis, 5 days per week. **Primed:** An active priming stimulation was first provided at 6 Hz for twenty trains of 5 seconds	**Outcomes measured:** MADRS, BDI, BPRS, CORE Rating of Psychomotor Disturbance, GAF, CGI, Edinburgh Handedness Inventory. **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks and 4 weeks. **Type of Analysis:** Intention to treat

		duration, at 90% of the MT, applied with a 25-second intertrain interval. Then 1 Hz rTMS at 110% of MT for one continuous, 15-minute train. Patients received 10 sessions of treatment on a daily basis, 5 days per week.	
Levkovitz[116] 2009 Israel	**Patient Selection:** Patients were recruited from 1 hospital between April 2006 and May 2008 and were randomized by computer generation **Inclusion Criteria:** Age 18-65, right-handedness, un ipolar depression, CGI-S score ≥4, HAMD-24 score ≥ 22. **Exclusion Criteria:** History of DSM-IV Axis I disorders apart from depression, severe personality disorder, hospitalization due to exacerbation related to borderline personality disorder, neurological disorder or medication therapy known to alter seizure threshold, epilepsy in first degree relatives, existence of metallic particles in the head or its vicinity, implanted cardiac pacemaker, implanted neurostimulators, surgical clips, cochlear implants or any medical pumps, prior treatment with TMS, electroconvulsive therapy <9 months prior to study entry, vagus nerve stimulator implant, history of a convulsive disorder of candidate or first degree relative of candidate, substantial suicidal risk or attempted suicide in the past year, participation in a clinical study within 30 days prior or concurrent to this study, drug abuse or alcoholism in the past year, pregnancy or lack of a reliable method of birth control. **Patient Characteristics:** Twenty-three patients with a mean age of 45.6 (13.3), 11 females and 12 males were randomized to deep brain stimulation preferentially left-sided low intensity rTMS. Twenty-two patients with a mean age of 45.8 (12.0), 11 females and 11 males were randomized to deep brain stimulation bilateral low intensity rTMS. Eleven patients with a mean age of 44.3 (11.4), 7 females and 4 males were randomized to deep brain stimulation left-sided high intensity rTMS. Eight patients with a mean age of 49.9 (9.5), 5 females and 3 males were randomized to deep brain stimulation left-sided high intensity rTMS. **Definition of Treatment Resistance:** Failed at least 2 trials of antidepressants medications.	**Deep brain left:** 20 Hz at 110% MT for 42 trains (1680 pulses per session) 5 days/week for 4 weeks. **Deep brain bilateral:** 20 Hz at 110% MT for 42 trains (1680 pulses per session) 5 days/week for 4 weeks. **Deep brain left 110%:** 20 Hz at 120% MT for 42 trains (1680 pulses per session) 5 days/week for 4 weeks. **Deep brain left 120%:** 20 Hz at 120% MT for 42 trains (1680 pulses per session) 5 days/week for 4 weeks.	**Outcomes measured:** HAMD, CGI, PSQI, CANTAB. **Follow-up time:** 3 months **Outcome ascertainment:** baseline, 1 week, 2 weeks, 3 weeks, 4 weeks, 3 months. **Type of Analysis:** Intention to treat
McDonald[55] 2006 United States	**Patient Selection:** Patients were recruited from the community (recruitment dates not reported) and were randomized (method not reported). **Inclusion Criteria:** SCID criteria for Unipolar Depression (UP) or Bipolar Disorder (BP), depressed phase, and HAMD-17 > 20. **Exclusion Criteria:** Evidence of dementia on neuropsychological testing or meeting SCID criteria for Organic Brain Syndrome, Organic Mood Disorder, Substance Dependence within the last 6 months, a diagnosis of a significant central neurological disorders, pregnancy, the presence of cardiac pacemakers, cochlear implants, or other intracranial implants with the exception of dental fillings, presence of psychiatric symptoms of significant severity, requirement of continued treatment with antidepressant medications, acute, unstable medical conditions, previous TMS. **Patient Characteristics:** Twenty-five patients with a mean age of 49.0 (SD not reported), 18 females and 7 males received left-sided high frequency then right-sided low frequency rTMS. Twenty-five patients with a mean age of 49.0 (SD not reported), 9 females and 16 males received right-sided low frequency then left-sided high frequency rTMS. **Definition of Treatment Resistance:** Failed at least 3 trials of antidepressants medications during the current episode.	**Left-sided high frequency/right-sided low frequency:** 10 Hz rTMS to left DLPFC at 110% MT for 20 trains (1000 pulses) followed by 1 Hz to right DLPFC at 110% MT for 20 trains (600 pulses) for 5 days/week for 2 weeks. **Right-sided low frequency/left-sided high frequency:** 1 Hz rTMS to right DLPFC at 110% MT for 20 trains (600 pulses) followed by 10Hz to left DLPFC at 110% MT for 20 trains (1000 pulses) for 5 days/week for 2 weeks.	**Outcomes measured:** HAMD, CGI, BDI, BPRS. **Follow-up time:** 3 months **Outcome ascertainment:** Baseline, 2 weeks, 1 month , 2 months, 3 months **Type of Analysis:** Intention to treat
Rybak[113] 2005, Australia	**Patient Selection:** Participants were recruited from 1 hospital and private outpatient clinics (recruitment dates not reported) and were randomized by order of presentation **Inclusion Criteria:** Right handedness, 20-75 years of age, suffering DSM-IV major depressive episode (unipolar or bipolar) with a HAMD-17 score ≥ 18, clinical circumstances indicating that a physical treatment would be an appropriate next step. **Exclusion Criteria:** A history of epilepsy, concurrent serious medical illness, alcohol or drug abuse, and presence of intracranial metal objects.	**Standard:** 20 Hz rTMS to left DLPFC at 100% of MT, for 30 2s trains, followed by 200 1 Hz placebo to right DLPFC. Each patient received 1200 stimuli at each treatment session. Stimulation was provided for ten days over two weeks. **Experimental:** 20 Hz rTMS to left DLPFC at 100% of MT for 25 2s trains, followed by 200 1 Hz	**Outcomes measured:** HAMD, VAS. **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, 1 week, and 2 weeks. **Type of Analysis:** NR

	Patient Characteristics: Nine patients with a mean age of 53.4 (13.3), 6 females and 3 males were randomized to standard rTMS. Nine patients with a mean age of 47.0 (12.3), 6 females and 3 males were randomized to experimental rTMS. **Definition of Treatment Resistance:** Failure to respond to at least a four week trial at maximum recommended doses of medication from at least one family of antidepressants.	stimulations to right DLPFC. Each patient received 1200 stimuli at each treatment session. Stimulation was provided for ten days over two weeks.	

BDI Beck Depression Inventory; **CGI** Clinical Global Impression; **DLPFC** Dorsolateral Prefrontal Cortex; **DSM** Diagnostic and Statistical Manual; **ECT** Electroconvulsive Therapy; **HAMD** Hamilton Depression Rating Scale; **Hz** Hertz; **MADRES** Montgomery-Asberg Depression Rating Scale**; MT** Motor Threshold; **NR** Not reported; **rTMS** Repetitive Transcranial Magnetic Stimulation

5.3.8.2 Quality of Included Studies

Each of the 13 RCTs had areas where the risk of bias was low and unclear (**Table 16**). There were only four studies which were assessed as having a high risk of bias in one of the seven areas[71;107;115;116]. All of the included studies used some type of randomization to allocate participants to either the rTMS or sham arm. However, five of the included studies did not report the method of randomization, and therefore it was not possible to assess random sequence generation; these studies were given an "unclear" risk in this category[55;69;71;107;113]. The remaining eight studies were assessed as having a "low" risk of bias due to random sequence generation[83;93;108;111;112;114-116]. Due to unclear methods, it was difficult to assess allocation concealment, and all but one study[83] received an "unclear" risk of bias in this category.

Nine of the studies had "unclear" risk of bias for blinding of participants and personnel[55;69;71;83;93;108;111-113], three had a high risk of bias[107;115;116], and one had a low risk of bias for this category[114]. All of the included studies except three used a blind outcome assessor; of the remaining three, two were not clear on whether the assessor was blind[69;71] and another had a high risk of bias in this area due to not having a blinded assessor[115].

All included studies had complete outcome data (making the risk of bias due to incomplete data outcome low), and showed no evidence of selective reporting, with the exception of Pascual-Leone et al.[71] It is unknown whether other biases influenced the results of these studies. Due to this, "unclear risk of bias" was assigned to all included studies under the category "Other Bias."

Table 16: Quality Assessment of rTMS versus other rTMS Studies as Assessed by the Cochrane Risk of Bias[35]

Author	Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Any other bias?
Conca[107]	2002	Unclear	Unclear	High	Low	Low	Low	Unclear
Fitzgerald[114]	2009a	Low	Unclear	Low	Low	Low	Low	Unclear
Fitzgerald[108]	2008	Low	Unclear	Unclear	Low	Low	Low	Unclear
Galletly[115]	2012	Low	Unclear	High	High	Low	Low	Unclear
Garcia-Toro[69]	2006	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Levkovitz[116]	2009	Low	Unclear	High	Low	Low	Low	Unclear
McDonald[55]	2006	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Paillere Martinot[83]	2010	Low	Low	Unclear	Low	Low	Low	Unclear
Pascual-Leone[71]	1996	Unclear	Unclear	Unclear	Low	Low	High	Unclear
Price[112]	2010	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Rybak[113]	2005	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Triggs[93]	2010	Low	Unclear	Unclear	Low	Low	Low	Unclear
Turnier-Shea[111]	2006	Low	Unclear	Unclear	Low	Low	Low	Unclear

5.3.8.3 Narrative Synthesis of Studies

5.3.8.3.1 Image Guidance

Three of the included studies investigated the use of image guidance in rTMS on response rates for TRD.[69;83;106] Image guidance was considered to be any form of radiological imaging used to guide the localization of rTMS stimulation and included techniques such as magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET).

Two of these studies compared patients treated with a standard rTMS protocol (without the use of image guidance) to those with either SPECT-guided rTMS or PET-guided rTMS. While no operational definition of response to treatment was provided in the study examining the use of SPECT-guided rTMS, the authors found that following 10 stimulation sessions the number of patients exhibiting more than a 50% decrease in HAMD scores was the same between the standard rTMS and SPECT-guided rTMS groups (n=2 for each group)[69]. In the study examining the use of PET-guided rTMS, the proportion of reported responders was the same in the standard rTMS (10/18 patients) and the PET-guided rTMS (8/16 patients) following 10 days of treatment. Neither of these two studies reported rates of remission among their study populations[83].

In the remaining study, all patients underwent MRI scans followed by one of two different mechanisms for stimulation localization of the DLPFC: a standard localization technique and a neuro-navigational technique based off structural images. Broadly, the standard localization—also known as the 5 cm method—involved localization of the motor cortical site for optimal stimulation of a hand muscle and then measurement 5 cm anteriorly along the scalp. In contrast, the neuro-navigational method involved localization of a brain site identified on an MRI scan from a patient performing specific tasks as well as in relation to gyral landmarks. Response to treatment was defined as a greater than 50% reduction from the baseline MADRS score. At 1-month follow-up, 5 out of 27 patients in the 5 cm method group were identified as responders, whereas 10 out of 24 patients responded to treatment in the neuro-navigational group. Remission following treatment, which was not defined in this study, was achieved by 3 patients in the 5 cm method group as well as 5 patients in the neuro-navigational group. These differences in the response and remission rates were statistically significant[106].

5.3.8.3.2 Right versus Left Dorsolateral Prefrontal Cortex Stimulation

Two of the included studies investigated the impact that the side of stimulation (i.e. right or left DLPFC) may have on the efficacy of rTMS for TRD[71;93]. Neither response to treatment nor remission following treatment was defined for these studies.

One study was designed as a multiple cross-over, placebo-controlled RCT that included four treatment scenarios: left-sided rTMS, right-sided rTMS, left-sided sham stimulation, right-sided sham stimulation. After 1 week of treatment, the mean HAMD scores reported for patients receiving left DLPFC rTMS was significantly lower compared to the other treatment groups, including right DLPFC rTMS[71].

In the second study, patients were randomized to receive rTMS stimulation to either the right DLPFC or left DLPFC, provided at the same frequency and intensity levels. Following a protocol of 2 week stimulation, patients receiving right-sided rTMS tended to achieve lower HAMD scores in comparison to patients receiving left-sided rTMS; however, this difference was not statistically significant. Rates of remission were not reported for either study[93].

5.3.8.3.3 Scheduling

Two of the included studies examined how spacing or temporal differences in stimulation throughout the course of rTMS treatment would influence the rates of response and remission in patients with TRD[110;111]. In each study, the duration of rTMS treatment was comparable between treatment groups, but the number of days in between sessions was varied.

One small study included only 16 patients for 2 weeks of treatment. Patients were randomized to receive daily rTMS with 10 sessions, 5 days/week or spaced rTMS consisting of 5 sessions with 3 treatments in week one, and 2 treatments in second week. The rates of response, defined as a 50% reduction in HAMD scores, were similar between the daily rTMS (n=2) and the spaced rTMS (n=3) by the completion of treatment. Among all of the patients, only 1 individual from the spaced rTMS group achieved remission, defined as a HAMD score of 8 or less[111].

The second study was much larger (n=77) and compared spaced rTMS (i.e. stimulation applied 3 days/week) versus daily rTMS (i.e. stimulation applied 5 days/week) for a total of 18 and 20 sessions, respectively. The number of individuals responding to treatment, defined as a reduction in HAMD scores below 50% of baseline was not significantly different between spaced rTMS (n=18) and daily rTMS (n=15) groups. Of these individuals, the number achieving remission or a final HAMD score of 8 or less, was also not significantly different between the spaced rTMS (n=14) and the daily rTMS (n=11) groups[110].

5.3.8.3.4 Electroencephalography-timed

One study investigated the use of electroencephalography (EEG) to guide the timing of rTMS for patients with TRD[112]. In comparison to a standard treatment group (no EEG guidance), this technology offered an interactive technique to time the delivery of individual stimuli based on the background EEG activity. Response was defined as a reduction of 50% of more in HAMD scores and the criteria for remission was a final HAMD score of 8 or less. With the standard treatment as the referent group, the odds ratio for response was 2.70 (95% CI: 0.7-10.1), and for remission was 1.48 (95% CI: 0.3-6.5). While the point estimates suggest that there are greater odds of response and remission for individuals in the Experimental or EEG-timed group, this was not statistically significant.

5.3.8.3.5 Combination Protocols

A number of studies compared rTMS protocols that differed by two or more concomitant properties, including stimulation intensity, frequency, sided-ness, sequence, and timing. In total, 5 studies investigated the impact of these combination rTMS protocols on response and remission rates for patients with TRD[55;107;108;113;116].

Three studies investigated the augmentation properties of rTMS by combining low and high frequencies, application to different DLPFC sides, and varying sequences of stimulation. In one study, 36 patients were randomized to three rTMS protocols: high-frequency left followed by low-frequency right rTMS (High/Low 1); alternating high-frequency left and low-frequency left rTMS (High/Low 2); and high-frequency left rTMS alone (High). Following 5 days of treatment the rates of response, defined as a CGI score greater than 4, were not significantly different between all three treatment groups (n=6 for High/Low 1; n=8 for High/Low 2; n=10 for High). Remission rates were not reported in this study[107]. The second study compared two rTMS protocols that differed primarily in their sequence of stimulation: high-frequency left rTMS (left high) followed by low-frequency right rTMS; and low-frequency right rTMS followed by high-frequency left rTMS. The number of responders, defined as those with a 50% of more reduction in HAMD scores, was greater in the left-sided high frequency/right-sided low frequency group (n=7) compared to the right-sided low frequency/left-sided high frequency group (n=3). This difference, however, was not statistically significant. Among all responders, there were only 3 remitters or those with final HAMD scores of 7 or less, all from the high frequency/right-sided low frequency rTMS group[55]. The third study examined whether an initial course of high-frequency rTMS treatment could be enhanced with a second course of low-frequency right rTMS (experimental rTMS). Patients receiving the experimental treatment paradigm were compared to those treated with an initial course of high-frequency rTMS treatment, followed by right placebo rTMS (standard rTMS). In this small study (n=18), response was defined as a 50% reduction in HAMD scores. The number of responders was comparable between the experimental (n=6) and standard (n=5) rTMS groups. Similarly the rates of remission, defined as a final HAMD score of 8 or less, were 56% (5/9) and 44% (4/9) for the Experimental and Standard rTMS groups, respectively. The response and remissions were not significantly different between treatment groups[113].

One study compared 4 deep brain rTMS protocols that differed in laterality (unilateral versus bilateral) and intensity (as a percentage of motor threshold) of stimulation and included: deep brain left rTMS; deep brain bilateral rTMS; deep brain low-intensity (110%) left rTMS; and deep brain high-intensity (120%) left rTMS.

Response to treatment was defined as a 50% or more reduction in HAMD scores. By the 5-week time point, 47% (9/19) of patients in the deep brain left rTMS group, 30% (6/20) of the patients in the deep brain bilateral rTMS group, 60% (6/10) of patients in the deep brain high-intensity left group, and no patients (0/8) in the deep brain low-intensity left group reached the criteria for response. The remission rates, defined as a final HAMD score less than 10, were 42% (8/19) for patients in the deep brain left rTMS group, 10% (2/20) for patients in the deep brain bilateral rTMS group, 50% (5/10) for patients in the deep brain high-intensity left group and zero for patients in the deep brain low-intensity left group. These differences in response and remission were statistically significant, suggesting superior efficacy of the higher intensity treatments as well as left rather than bilateral stimulation[116].

Another study investigated whether a higher-frequency priming rTMS would enhance the efficacy of low-frequency rTMS. Patients were randomized to either non-primed (sham-priming) or primed rTMS treatment. Response was defined as a greater than 50% reduction in MADRS score. Four months following treatment, 10 patients (33%) in the primed rTMS group and 4 patients (14%) in the sham-priming group achieved the criteria for response. This difference was not statistically significant. Remission rates were not reported for this study[108].

5.3.8.4 Conclusion

There is substantial experimentation to identify and improve the optimal rTMS protocol. Active research is ongoing with the use of image-guided techniques, scheduling of treatment, timing of treatment and deep brain stimulation. None of these research areas are developed enough to clarify the role of these variables in the effective use of rTMS.

5.3.9 Repetitive Transcranial Magnetic Stimulation Compared to Electroconvulsive Therapy

5.3.9.1 Characteristics of Included Studies

Six RCTs comparing rTMS with ECT were included [117-122]. Of these studies, two were conducted in Australia[119;120], one was conducted in Brazil[122], one was conducted in Iran[121], one was conducted in Israel[117] and one was conducted in the United States[118]. Five of the six RCTs compared an rTMS arm to an ECT arm[117;118;120-122], while one compared a combination of rTMS and ECT to ECT alone[119]. The definition of treatment resistance varied by study; two studies defined treatment resistance as failure to respond to at least

one adequate trial of antidepressant treatment[117;120], three studies defined treatment resistance as failure to respond to at least two adequate trials of antidepressant treatment[119;121;122], and one study did not report their definition of treatment resistance[118].

Additional characteristics of the included studies have been summarized in **Table 17**.

Table 17: Characteristics of Studies Assessing the Efficacy of rTMS versus ECT

Author, Year of Publication, Country	*Patient Selection*	*Comparators*	*Outcomes*
Grunhaus[117] 2003, Israel	**Patient Selection:** Participants were recruited from the Psychiatry Division at the Sheba Medical Center, and had been referred for ECT. **Inclusion Criteria:** Diagnosis of unipolar major depression by DSM-IV, score of at least 18 on Hamilton Depression Rating Scale, 18 years or older, treatment resistant **Exclusion Criteria:** Additional Axis I diagnoses, major depression with psychosis, major depression due to medical condition or substance abuse **Patient Characteristics:** Twenty other participants were randomized to receive rTMS (14 female, 6 male) with a mean age of 57.6(13.7). Twenty participants were randomized received ECT (15 female, 5 male), with a mean age of 61.4(16.6). **Definition of Treatment Resistance:** Failure to respond to at least 1 adequate trial of antidepressant treatment.	**Type of rTMS** 10 Hz rTMS, delivered at 90% motor threshold to the left dorsolateral prefrontal cortex 5 days per weeks over 4 weeks (1,200 pulses per day, 24,000 total over rTMS treatment). **Type of Comparator** ECT conducted using the guidelines of the American Psychiatric Association. Participants were given 1mg/kg methohexital and .75mg/kg succinylcholine. Treatments were performed at 2.5 times threshold charge, and increased by 10-20% to maintain seizure length of at least 25 seconds.	**Outcomes measured:** Hamilton Depression Rating Scale, Brief Psychiatric Rating Scale, Global Assessment of Function Scale, Global Depression Scale, Pittsburgh Sleep Quality Index, Mini-Mental State Examination **Follow-up time:** 4 weeks **Outcome ascertainment:** Baseline, 2 weeks, end of treatment (4 weeks **Type of Analysis:** Not reported
Janicak[118] 2002, United States	**Patient Selection:** Not reported **Inclusion Criteria:** Age 18-75, met DSM-IV criteria for unipolar or bipolar major depression, clinically appropriate for course of ECT, score of at least 20 on the Hamilton Depression Rating Scale, treatment resistant **Exclusion Criteria:** None reported **Patient Characteristics:** Thirteen participants were randomized to receive rTMS. Nine participants were randomized to receive ECT with a mean age of 42.73(14).There were no statistically significant differences in age. **Definition of Treatment Resistance:** Not Reported	**Type of rTMS** 10 Hz rTMS, delivered at 110% motor threshold to the left dorsolateral prefrontal cortex five times per week for 10-20 sessions (1,000 stimulations per session) **Type of Comparator** ECT three times per week for 3-12 bitemporal treatments. Participants were given 1mg/kg of methohexital and 1mg/kg succinylcholine	**Outcomes measured:** Hamilton Depression Rating Scale, Brief Psychiatric Rating Scale, Young Mania Rating Scale, Clinical Global Impression Scale. **Follow-up time:** End of treatment (between 2-4 weeks) **Outcome ascertainment:** Baseline, weekly, end of treatment **Type of Analysis:** Not reported
Keshtkar[121] 2011, Iran	**Patient Selection:** Patients who were referred for ECT were recruited from southwestern Iran and randomized to receive rTMS or ECT by coin toss. **Inclusion Criteria:** Diagnosis of major depressive disorder by DSM-IV **Exclusion Criteria:** previous rTMS, implanted device, history of seizure, bipolar disorder, substance abuse, history of significant head trauma, severe medication condition, previous nonresponse to ECT, pregnancy **Patient Characteristics:** Thirty three participants (20 females, 13 males), mean age 34 (9.9) were randomized to receive rTMS. Forty participants (32 female, 8 male), mean age 35.6(8.1) were randomized to receive ECT. **Definition of Treatment Resistance:** Failure to respond to at least 2 adequate trials of antidepressant treatment.	**Type of rTMS** rTMS to the left dorsolateral prefrontal cortex delivered at 90% motor threshold for 10 sessions (408 simulations per session for a total of 4080 stimulations per patient) **Type of Comparator** bilateral ECT with constant current for 10 sessions (3 times per week). Seizures were at least 20 seconds in length. Participants were given Thiopental and Succinylcholine.	**Outcomes measured:** Beck Depression Inventory, Hamilton Depression Rating Scale **Follow-up time:** Post-intervention (with the intervention period ranging from 10d for rTMS and 3weeks and 1 day for ECT) **Outcome ascertainment:** Baseline, and post-intervention **Type of Analysis:** Per protocol
Pridmore[119] 2000, Australia	**Patient Selection:** Patients were drawn from out-patient, in-patient, public and private service. **Inclusion Criteria:** Treatment resistant, DSM-IV diagnosis of major depressive disorder, right-handed, age 25-70, no history of epilepsy **Exclusion Criteria:** Intracranial metal objects **Patient Characteristics:** Eleven participants were randomized to receive rTMS (6 females, 5 males) with a median age of 48. Eleven other participants were randomized to receive ECT (5 females, 6 males) with a median age of 46. The two groups did not differ in age or gender.	**Type of rTMS** Two cycles of 1 day ECT followed by 4 days rTMS. 20 Hz rTMS, at 100% motor threshold.. **Type of Comparator** Unilateral ECT 3 times per week for 2 weeks. Participants were given 1-1.5mg/kg methohexitonium and 0.5mg/kg suxamethonium	**Outcomes measured:** Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale, Visual Analogue Scale, Global Assessment of Functioning Scale, Side-effects scale **Follow-up time:** 2 weeks **Outcome ascertainment:** Baseline, week 1, week 2

	Definition of Treatment Resistance: Failure to respond to at least one month trial of two families of antidepressant medications, at the manufacturers recommended maximum dosage.		**Type of Analysis:** Not reported
Pridmore[120] 2000, Australia	**Patient Selection:** Consecutive patients at the Royal Hobart Hospital, who met the inclusion criteria, were invited to participate **Inclusion Criteria:** DSM-IV major depressive episode, score of at least 18 on the Hamilton Depression Rating Scale, treatment resistant, right-handed, no history of epilepsy **Exclusion Criteria:** Serious medical illness, intracranial metal objects, mood disorder due to medical condition or substance abuse, co-morbidity for mental disorder **Patient Characteristics:** Sixteen participants (12 females, 4 males), mean age 44(11.9) were randomized to receive rTMS. Sixteen participants (13 females, 3 males), mean age 41.5(12.9) were randomized to receive ECT. **Definition of Treatment Resistance:** Failure to respond to at least one 4 week trial of antidepressants at the maximum recommended dose.	**Type of rTMS** 20 Hz rTMS using 100% motor threshold delivered to the left prefrontal cortex for five days per week. **Type of Comparator** ECT 3 days per week on non-dominant hemisphere. Participants were given 1-1.5 mg/kg methohexitone and 0.5 mg/kg suxamethonium	**Outcomes measured:** Hamilton Depression Rating Scale, Beck Depression Inventory, Visual Analogue Scale, Side-effects scale **Follow-up time:** Last treatment **Outcome ascertainment:** Baseline, 3 times per week during treatment and end of study **Type of Analysis:** Not reported
Rosa[122] 2006, Brazil	**Patient Selection:** Patients were recruited by physician referral at the Psychiatric Institute of the University of Sao Paulo **Inclusion Criteria:** Age 18-65, DSM-IV diagnosis of unipolar depressive disorder, score of at least 22 on the Hamilton Depression Rating Scale, treatment resistance **Exclusion Criteria:** Psychotic symptoms, history of epilepsy, history of neurosurgery with metal clips, co-morbid neurological or psychiatric diseases, cardiac pacemaker, pregnancy **Patient Characteristics:** Eight participants (7 female, 8 male), mean age 46(10.6) were randomized to receive ECT. Eight participants (12 female, 8 male), mean age 41.8(10.2) were randomized to receive rTMS. **Definition of Treatment Resistance:** Failure to respond to at least 2 antidepressants in difference classes (used for at least 4 weeks with adequate dosages), with augmentation (with lithium or thyroid hormone for at least one trial).	**Type of rTMS** 10 Hz rTMS at 100% motor threshold to the left prefrontal area 5 times per week for 4 weeks (2500 stimulations per session, 50,000 stimulations total) **Type of Comparator** right unilateral ECT conducted using the guidelines of the American Psychiatric Association. Participants were given 1-1.5mg/kg etomidate, 0.5-1.25mg/kg succinylcholine and 0.4-1.0 mg atropine.	**Outcomes measured:** Hamilton Depression Rating Scale, Visual Analogue Scale, Clinical Global Impression **Follow-up time:** End of treatment (4 weeks) **Outcome ascertainment:** Baseline, 2 weeks, end of treatment **Type of Analysis:** Intention-to-treat

DSM Diagnostic and Statistical Manual; **ECT** Electroconvulsive Therapy; **Hz** Hertz; **rTMS** Repetitive Transcranial Magnetic Stimulation

5.3.9.2 Quality of Included Studies

Each of the RCTs assessing rTMS versus ECT had areas where the risk of bias was low and unclear (**Table 18**). Three of the included studies also had areas where the risk of bias was high[117;120;121]. Since all studies were randomized controlled trials, all used some type of randomization to allocate participants to either the rTMS or sham arm. However, two of the included studies did not report the method of randomization, and therefore it was not possible to assess the random sequence generation bias in these studies. The risk of bias due to blinding was mixed across the included studies, with some studies not blinding personnel, participants and/or outcome assessors.

Five of the six included studies had complete outcome data (making the risk of bias due to incomplete data outcome low), and none showed evidence of selective reporting. It is unknown whether other biases influenced the results of these studies. Due to this, "unclear risk of bias" was assigned to all included studies under the category "Other Bias."

Table 18: Quality Assessment of rTMS versus ECT Studies as Assessed by the Cochrane Risk of Bias[35]

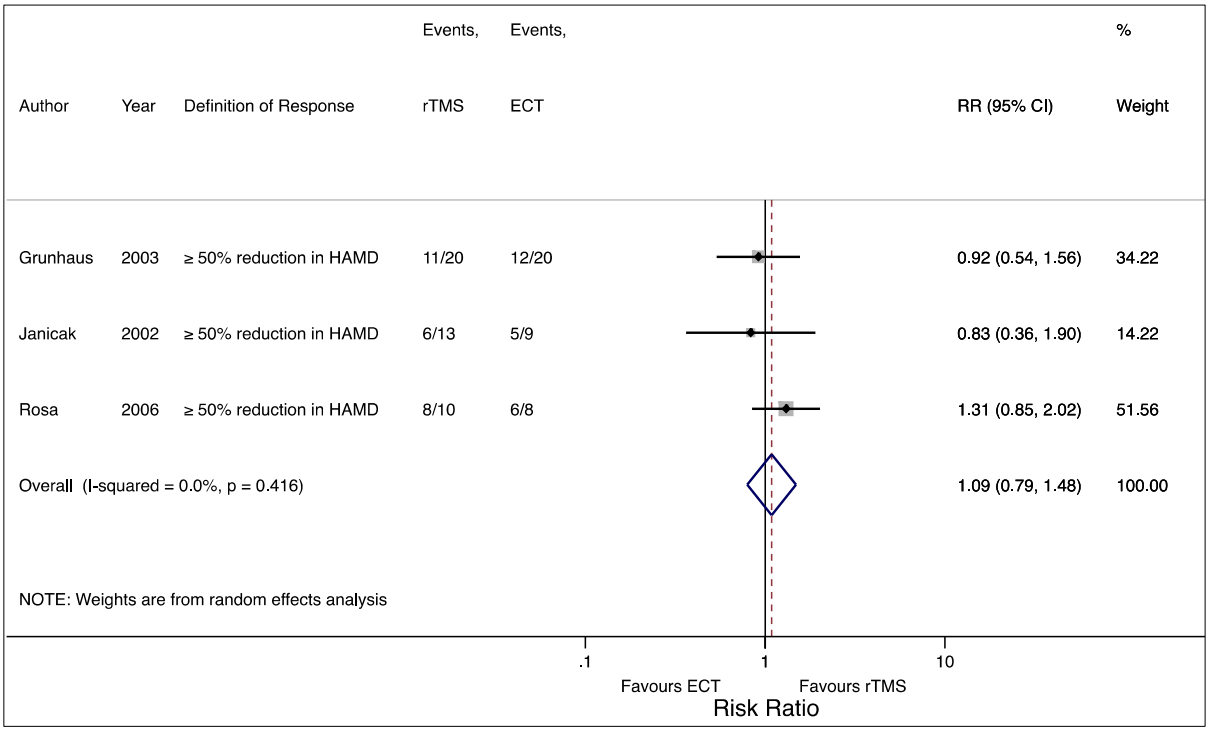
Author	**Year**	**Random Sequence Generation**	**Allocation Concealment**	**Blinding of Participants and Personnel**	**Blinding of Outcome Assessment**	**Incomplete outcome data**	**Selective reporting**	**Any other bias?**
Grunhaus[117]	2003	Low	Unclear	High	Low	Unclear	Low	Unclear
Janicak[118]	2002	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Keshtkar[121]	2011	Low	Unclear	High	High	Low	Low	Unclear
Pridmore[119]	2000a	Unclear	Unclear	Low	Low	Low	Low	Unclear
Pridmore[120]	2000b	High	High	High	Low	Low	Low	Unclear
Rosa[122]	2006	Low	Unclear	Unclear	Low	Low	Low	Unclear

5.3.9.3 Meta-analysis of Treatment Response

Three rTMS versus ECT studies provided adequate data on treatment response to permit pooling[117;118;122]. **Figure 15** shows the response results (forest plot) for rTMS compared to ECT. The definition of response as defined by each paper's authors was used in this analysis. All three papers used the HAMD to determine response, and all used a cut off of at least 50% reduction in depression score as their definition.

The overall pooled risk ratio for rTMS versus ECT is 1.09 (95% CI: 0.79-1.48). This pooled estimate suggests that patients may be more likely to experience treatment response with rTMS than with ECT. However, the results are not statistically significant different; rTMS may be less or more effective compared to ECT.

Figure 15: Forest Plot of Response in Patients Receiving rTMS versus those receiving ECT Treatment

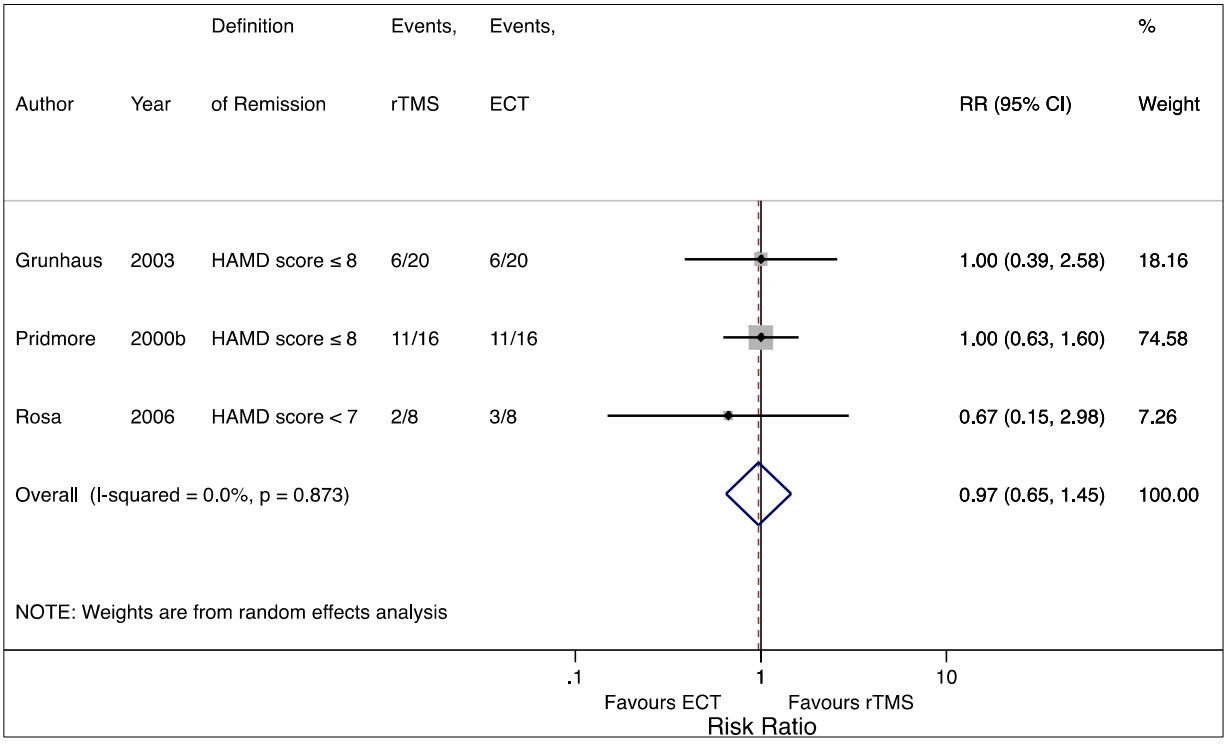


5.3.9.4 Meta-analysis of Remission

Three of the rTMS versus ECT studies provided adequate data on treatment remission to permit pooling[117;120;122]. **Figure 16** shows the remission results (forest plot) for rTMS compared to ECT. The definition of remission as defined by each paper's authors was used in this analysis. Therefore, the scale remission varied by paper, as shown in the **Figure 16**. All three of these studies used the HAMD to define remission; however, two used a threshold score of 8, and one used a threshold score of 7[117;120;122].

The overall pooled risk ratio for rTMS versus ECT remission rate is 0.97 (95% CI: 0.65-1.45). This pooled estimate suggests that patients may be more likely to experience remission with ECT than with rTMS treatment. However, as the CI of this pooled estimate crosses the null line (1.00), this effect is not statistically significant. This result therefore suggests that there is no statistically significant difference in remission rate of patients treated with rTMS compared to those treated with ECT.

Figure 16: Forest Plot of Remission in Patients Receiving rTMS versus those receiving ECT Treatment



5.3.9.5 Safety of rTMS compared to ECT

The only adverse effects reported in the six included studies assessing rTMS versus ECT were pain/discomfort and headache. Three studies reported some of their patients had headaches[117;118;121]; all reported that the headaches subsided quickly. Only one study reported rates of patient pain/discomfort[118]. In this study, six participants in the rTMS arm reported pain and/or discomfort, and no patients in the ECT group reported pain or discomfort[118]. None of the included studies reported serious adverse events such as cognitive impairment or seizure.

5.3.9.6 Conclusions on Repetitive Transcranial Magnetic Stimulation Compared to Electroconvulsive Therapy

The effectiveness of rTMS compared to ECT is unclear. There is a trend towards rTMS being more effective to achieve clinical response but less effective to achieve remission. However, as this result is not statistically significant, ECT may be less effective, equivalent or more effective compared to rTMS. No serious safety concerns were assessed; the most common side effects were headaches and pain/discomfort and appear to be equivalent between rTMS and ECT.

5.4 Discussion

The clinical efficacy systematic review identified 70 relevant RCTs. Of these studies, forty-five compared rTMS and sham, fourteen compared high and low frequency rTMS, five compared unilateral and bilateral rTMS, three compared high and low intensity rTMS, thirteen compared standard rTMS with various other rTMS protocols and six compared rTMS and ECT. This body of evidence indicates that rTMS is approximately twice as effective as sham procedure although the optimal rTMS protocol remains unclear. rTMS does cause minor side effects such as headaches and discomfort. Major adverse events, such as seizure and suicide ideation, have not been assessed. In comparison to ECT, the effectiveness of rTMS remains unknown with conflicting results; rTMS may be more effective to achieve response but less effective to achieve remission.

Within the identified literature, there is significant heterogeneity in rTMS protocols, duration of follow-up periods, reported outcome measures, control or comparison groups, and study quality and size. This may limit the robustness of our findings. However, no statistically significant differences were found between protocol differences such as high and low frequency, unilateral and bilateral treatment and high and low intensity, thus it is unlikely that pooling the mixed protocols would have introduced significant bias.

Broadly, the included studies were of moderate quality, with most having a combination of unclear and low risks of bias, and few having high risks of bias, as assessed by the Cochrane risk of bias[35]. Blinding of participants and treatment providers was an area where the included studies often suffered from a lack of clarity. Methods of random sequence generation were also largely unclear in the included studies. However, given that very few studies had a "high" risk in this area and most were "unclear", these areas of bias could have been due to a lack of detail in methods descriptions rather than an area of bias.

The majority of the included studies were conducted in the United States, and Australia, with very few studies conducted in Canada. However, there is no reason to suspect that the patient mix and underlying etiology of MDD and TRD are substantially different in Canada. Thus, we anticipate our findings being generalizable to the Canadian context.

Lastly, the outcomes reported within the RCTs included response and remission. While these outcomes are clinically robust outcomes, the desired outcome is the ability of the patient to return to living their life. Outcomes such as return to work and engagement in daily life are the relevant patient-centred outcomes. No evidence assessing these outcomes was identified.

While the optimal treatment protocol is yet to be established, rTMS is an effective treatment compared to sham with minor side effects. Its performance in comparison to ECT is not well understood. A large scale, well done RCT comparing rTMS to ECT is required.

6 Cost-Effectiveness and Economic Impact

Summary of Economic Evaluation Findings

- *rTMS is more costly and more effective than sham at achieving response and remission with a cost per QALY gained of $13,084 and $20,203, respectively.*
- *Comparing rTMS to ECT, rTMS is more effective and less costly than ECT the majority of the time for both response and remission.*
- *The estimated budget impact remains unknown; the total fixed investment required for 1 rTMS machine is $85,000 and the estimated marginal cost per procedure is $22.52.*
- *Additional data on the long-term impact of rTMS is required to support more in-depth modeling.*

6.1 Research Objectives

To determine the cost-effectiveness of rTMS compared to ECT and standard therapy

6.2 Review of Economic Literature

A literature review was completed to identify relevant economic studies comparing rTMS to ECT or standard therapy. Three relevant studies were identified and are briefly summarized.

In the United Kingdom, Knapp et al.[123] undertook a RCT comparing rTMS to ECT. They found that at the 6-month follow-up the mean total costs for rTMS (£7236) was significantly more than the cost of ECT (£3169) with similar clinical outcomes. Their overall conclusion was that ECT was more effective to treat TRD, and also had the potential to be more cost-effective than rTMS.

Kozel et al.[124] completed an economic model comparing ECT to rTMS. Using literature-based values, they compared three separate strategies: rTMS, ECT, and then rTMS followed by ECT for those not responding to rTMS (rTMS-to-ECT). Their model resulted in a cost per quality-adjusted life year (QALY) gained of $460,031 (US) for ECT compared to rTMS. When comparing ECT and rTMS to ECT alone the cost per QALY gained is $39,949. The study conclusions were that rTMS is more economically attractive than ECT.

The final study by Simpson et al.,[125] compared rTMS to sham treatment. The authors collected data from a multicenter study, RCT, comparing ECT to rTMS and subsequently performed an economic decision analysis. They found a cost per QALY gained of $34,999 (US) for rTMS during the RCT study. During the open label

follow-up, when rTMS was compared to what they deemed the standard of care, there was a cost savings of $1123 per QALY for rTMS. Overall, they concluded the rTMS is cost-effective, and can provide cost savings.

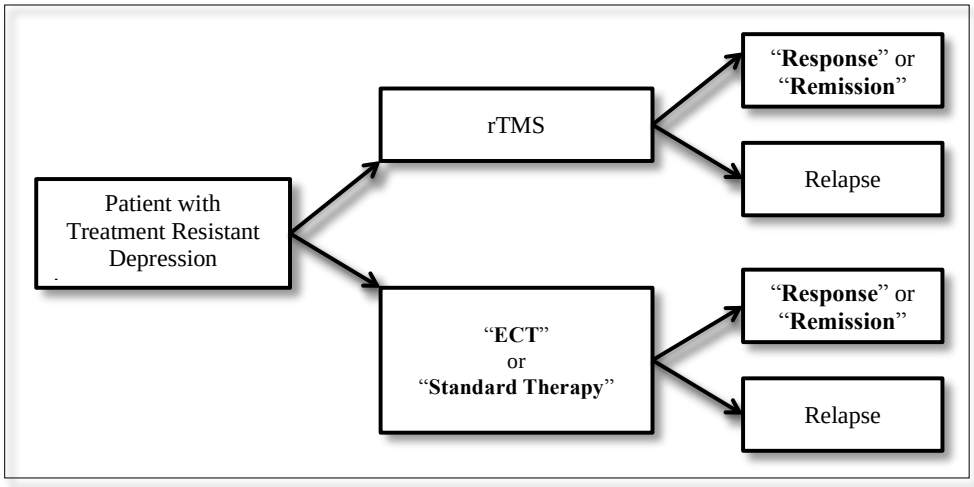
Current studies all have conflicting evidence reporting both an increased cost per QALY gained and cost savings with rTMS compared to ECT. The one study identified comparing rTMS to sham reports potential cost savings.

6.3 Methods

6.3.1 Economic Model

Simple decision models were created to compare rTMS to ECT and standard therapy. Given the lack of long-term data and other clinically relevant outcomes (suicide ideation, return to work, etc.), the model only considers response and remission **(Figure 17)**. The primary outcome for each model is the cost per QALY gained.

Figure 17: The overview of the model



6.3.2 Model Inputs

6.3.2.1 Perspective, Time Horizon, and Target Population

The perspective of the publically funded health care system is adopted. The target population is TRD patients with MDD who are eligible for rTMS. The time horizon adopted is 3-6 weeks as this is the longest duration of follow-up reported in the RCTs assessing clinical effectiveness. While a longer time horizon would be preferable to capture the likelihood of relapse or return to work, no data were available to support the long-term trajectory of this patient population.

6.3.2.2 Clinical Probabilities

Given the lack of long-term data on effectiveness and side effects, the only clinical outcomes considered were response or remission. Both probabilities were obtained from the clinical review (section 4). The included studies were meta-analyzed using a random effects model to obtain pooled estimates of response and remission for rTMS, ECT and standard therapy. The definition of remission and response were defined by the authors of each included study. Generally, response was defined as at least a 50% reduction from baseline scores and remission was defined as less than 8 on the HAMD or MADRS. The pooled probability of response and remission was calculated for ECT and standard therapy using the control arm in the RCTs. The pooled estimates of relative risk for rTMS were then applied to the probability of response and remission. For response, the probabilities for ECT and standard therapy are 0.622, and 0.119, respectively. The relative risks for rTMS were 1.09 for ECT and 2.35 for standard therapy **(Table 19).** For remission, the probabilities for ECT and standard therapy are 0.455, and 0.068, respectively, and relative risk for rTMS were 0.97 and 2.24 **(Table 19).**

Table 19: The individual probabilities of response and remission for each individual treatment course of standard therapy and ECT, with relative risks for rTMS

	Response	**Relative Risk rTMS Response (95% CI)**	**Remission**	**Relative Risk rTMS Remission (95% CI)**
Standard therapy	0.119	2.35 (1.70-3.25)	0.068	2.24 (1.53-3.27)
ECT	0.622	1.09 (0.79-1.48)	0.455	0.97 (0.65-1.45)

6.3.2.3 Costs

Only the costs of therapy were included in the model. Standard therapy was an average of three separate selective serotonin uptake inhibitors (SSRIs). The SSRIs were given for a standard dosage[126] for two treatment courses, as two failed treatment courses of 6 weeks is the general definition of treatment resistant depression. The costs of each generic form of individual medication were taken from the Alberta Interactive Drug Benefit List[127]; the generic drugs used were Citalopram ($0.2397 per 20 or 40mg pill), Paroxetine ($0.4513 per 20mg pill), and Fluoxetine ($0.4598 per 20mg pill). Using the aforementioned dosing schedule with two failed treatment courses the cost for standard therapy was $44.86 **(Table 20).**

The cost of one course of ECT was developed from a description of what is typically done in centers within Alberta, specifically the Centennial Centre in Ponoka, AB. The Alberta Health Services job board was used to estimate the costs of the time of the nurse involved in ECT[128]; given they spend 60 minutes in ECT this equated to $45.03 per session. The Anesthesiologist ($107.27) and Psychiatrist ($84.73) have a flat billing rate per session[129]. The cost of the machine per use was calculated using a cost for the machine of $70,000 with an average of 500 sessions per year, amortized over 10 years, with $13,000 in disposable airway tools costs; the cost of the ECT machine per use is $40. Given the average number of 12 sessions per initial course of treatment the total cost for ECT is $3,324.36 **(Table 20).**

There are two individuals normally involved in the administration of rTMS, the psychiatrist (who is only present at the first appointment) and the Registered Nurse. The psychiatrist will claim $84.72, in accordance with the schedule of medical benefits price list[129], and the Registered Nurse receives approximately $45.03 per hour and only allocates 30 minutes per patient[128]. The cost of the rTMS machine per use was taken from the Riverview Centre that performs rTMS, the amount they spent on the Magstim machine ($80,000 cost, and $5000 import fee), was divided by an average of 408 sessions per year, amortized over 10 years; this gives a cost of $20.83 per use. The costs of maintenance were not included as it was deemed negligible. Given an average administration of 20 sessions, the total cost of an initial course of rTMS is $951.70 **(Table 20).** Facility costs for ECT or rTMS were not included, as other programs would utilize the infrastructure in place if ECT or rTMS teams were not using them.

Table 20: The costs associated with each individual treatment course for standard therapy, ECT and rTMS

	Cost (CAN$)	Description	References
Standard therapy	45	Citalopram ($0.2397 per 20 or 40mg pill), Paroxetine ($0.4513 per 20mg pill), and Fluoxetine ($0.4598 per 20mg pill) costs averaged at 1 pill per day for two 6-week periods	(Drugs.com), (AIDBL)
ECT	3,324	Nurse at $45.03 per hour for an hour, Anesthetiologist $107.27 per session, and Psychiatrist $84.73 per session. Machine costs $70,000 over 10 years with an average of 500 sessions per year, and $13,000 in disposable airway tools per year. Estimated for initial 12 sessions of treatment.	(SOMB Price List), (AHS Job Board), (Ponoka)
rTMS	952	Nurse at $45.03 per hour for half an hour per session and Psychiatrist $84.73 for first session only. Machine costs $80,000 (extra $5,000 import fees), over 10 years with an average of 408 sessions per year. Estimated for initial 20 sessions of treatment.	(SOMB Price List), (AHS Job Board), (Riverview)

6.3.2.4 Utilities

There were three separate states within the models: response, remission, and depression. The utilities for these three states were extracted from literature from Revicki et al. [130] and McLoughlin et al.[10]; the utility for response was 0.73, remission was 0.83, and relapse (no response or remission attained) 0.30 **(Table 21).**

Table 21: The utilities associated with each mental health state

	Utility	Reference
Relapse (Continued Depression)	0.30	Revicki 1995[130]; McLoughlin 2006[10]
Response	0.73	Revicki 1995[130]; McLoughlin 2006[10]
Remission	0.83	Revicki 1995[130]; McLoughlin 2006[10]

6.3.3 Uncertainty Analysis

A sensitivity analysis was run on the relative risk of rTMS versus standard therapy and ECT for both response and remission; utilizing the 95% CIs associated with each relative risk the upper and lower limits were defined. A threshold analysis was run to determine at what cost rTMS may become the least cost-effective option.

A scenario analysis was conducted using the costs of informal care over the following 6-months for the comparison of ECT and rTMS. These cost estimates were taken from McLoughlin et al.[10], converted to Canadian dollars and the consumer price index was used to update them to 2013 Canadian dollars[131]. The total added to each was $696.81 for ECT and $5813.66 for rTMS.

The probabilistic sensitivity analysis (PSA) was run varying four separate parameters within each model to assess overall uncertainty: cost and relative risk of rTMS, and dependent on the model, the costs and probabilities of effectiveness of either standard therapy or ECT. A gamma distribution was used for costs, normal distributions were used for the relative risks of rTMS, and beta distributions were used for the probabilities of response and remission of standard therapy or ECT. The PSAs were run with samples of 1000 and the final probabilities that rTMS would be the most cost-effective option were reported.

6.4 Results

6.4.1 Standard therapy compared to repetitive transcranial magnetic stimulation

Compared to standard therapy, rTMS costs $907 more and is associated with 0.07 more QALYs gained considering response. Remission had the same cost increase, but a QALY gain of 0.04. The resulting cost per QALY gained with response is of $13,084 and remission $20,203 **(Table 22)**.

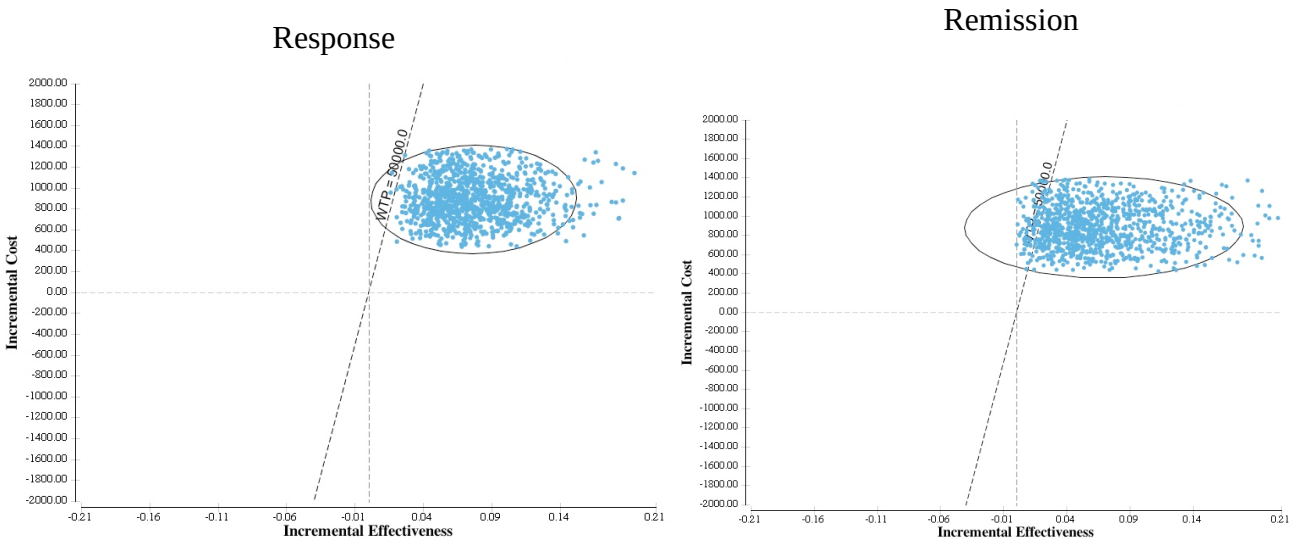
Table 22: Cost per quality-adjusted life year gained for Response and Remission of rTMS versus Standard therapy

	Cost ($)	**Incremental Cost ($)**	**Effectiveness (QALY)**	**Incremental Effectiveness (QALY)**	**ICER ($ per QALY)**
Standard therapy	45	0	Response: 0.35 Remission: 0.34	0	0
rTMS (Response)	952	907	0.42	0.07	13,084
rTMS (Remission)	952	907	0.38	0.04	20,203

6.4.1.1 Uncertainty Analysis

When the relative risk of rTMS was varied within the 95% CI, the cost per QALY gained with rTMS varied from $7,850 to $25,232 from response and $11,036 to $47,267 for remission. When rTMS costs $3,510, standard therapy becomes more cost-effective than rTMS for response and at a cost of $2,289, standard therapy is more cost-effectives at remission. The probabilistic sensitivity analysis of response indicates that 99.8% of the time rTMS is more costly and more effective than standard therapy **(Figure 18).** Considering remission, the probability that rTMS is more costly and more effective than standard therapy is 92.5% (**Figure 18).**

Figure 18: Incremental cost-effectiveness scatterplot resulting from the Probabilistic sensitivity analysis of Standard Therapy versus rTMS



6.4.2 Repetitive transcranial magnetic stimulation compared to Electroconvulsive therapy

Considering response, rTMS is less expensive and more effective than ECT (dominant, **Table 23*).*** When considering remission, ECT is more effective and more expensive than rTMS resulting in a cost per QALY gained of $328,325.

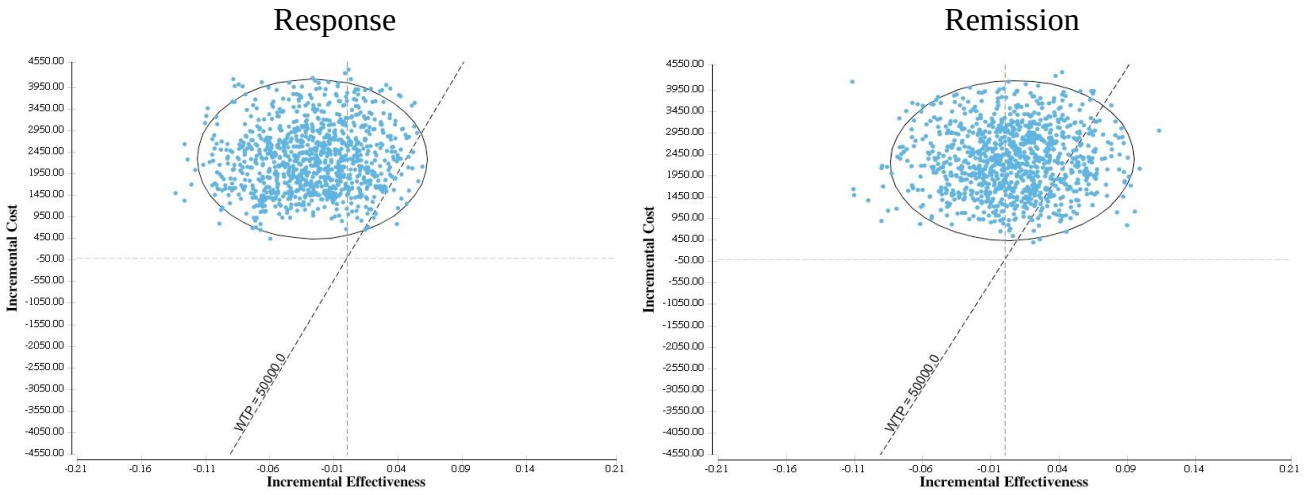
Table 23: Results of the cost-utility analysis of Response and Remission of rTMS versus ECT

	Cost ($)	Incremental Cost ($)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER ($ per QALY)
rTMS (baseline)	952	0	Response: 0.59 Remission: 0.53	0	0
ECT (response)	3324	2,373	0.57	-0.02	Dominated
ECT(remission)	3324	2,373	0.54	0.01	328,325

6.4.2.1 Uncertainty Analysis

When the relative risk of rTMS was varied within the 95% CI, rTMS varies from the less expensive and more effective (dominant) at the upper 95% CI bound for both response and remission to a cost per QALY gained of $42,270 for response and $28,142 for remission compared to ECT at the lower 95% CI bound. When rTMS costs $4,527, ECT becomes more cost-effective than rTMS for response and at a cost of $2,963, ECT is more cost-effectives at remission. When indirect costs associated with both ECT and rTMS are included, the cost per QALY gained ranges from $114,075 for response to rTMS being more expensive and less effective (dominated) for remission. The probabilistic sensitivity analysis of response indicates that 98.2% of the time ECT is less effective and more costly than rTMS **(Figure 19).** ECT is less costly and more effective 1.8% of the time. Considering remission, the probability that rTMS is the most cost-effective option 84.5% (**Figure 19).**

Figure 19: Incremental cost-effectiveness scatterplot resulting from the Probabilistic sensitivity analysis of ECT versus rTMS



6.4.3 Budget Impact Analysis

The number of patients with MDD who are TRD is unknown in Alberta. None of the key informants or available databases was able to provide a reliable estimate of the population size. Based on expert input from the Mental Health and Addictions Strategic Clinical Network, 7 rTMS machines (2 in each of Calgary and Edmonton and 1 in each of the North, Central and South Zones) would be required to support a provincial rTMS programme. We estimated the initial investment costs, and the subsequent procedural costs. The costs of standard therapy will vary for each patient depending on medication, dosage and length of treatment. However, the standard therapy costs are likely to be minimal compared to the treatment costs of rTMS or ECT.

The initial investment for ECT includes the purchase of the equipment to perform the procedure, which is approximately $70,000[132]. There is also the consideration of the facilities required to house the equipment and perform the procedure, and an approximate cost of $13,000 per year for airway equipment[132]; this cost is dependent on the number of procedures performed. For each procedure an anesthesiologist, nurse, and a psychiatrist must be present for the procedure; the anesthesiologist and psychiatrist have fixed charges for procedure, $107.27 and $84.73 respectively, while the nurse is paid an hourly rate of $45.03 (90,000/annum) [128;129]. These costs will rise with inflation, and a nurses salary will need to be paid independent of whether there

are procedures being performed or not. The total fixed investment is $160,000 and the marginal cost per procedure is $263.03.

rTMS requires a larger initial investment in the equipment, $85,500 for the machine, import fees and procedural chair, but the per procedure costs are lower as less staff is needed[133]. A psychiatrist is only required for the initial treatment and charges $84.73 per procedure[129]**.** The remaining staff required is a nurse, who is paid hourly ($45.03, $90,000/annum) independent of whether or not the procedures are being performed[128]. The total fixed investment is $175,500. The marginal cost for the first session is $132.33 and the marginal cost for ongoing sessions is $47.60 (accounting for 15 minutes of nursing time).

Given the current number of procedures completed in one clinic in Alberta per year (408 sessions) the cost of running the machine for one year is $19,415; this number is only the costs associated with treatments and the staff used during the treatments (**Figure 20**). The remaining cost of the nurse also needs to be taken into account, but it is unlikely that a full-time nurse would be allocated to rTMS; they would more likely be part-time and shared with another program, such as ECT. If the clinic in Alberta was to run at 70% capacity they would perform an estimated 286 sessions per year, the cost for an individual session would go up to $56.47, but the cost for running one machine for one year would be lower at $16,150.85. Similar results are seen when the estimates of utilization from NICE are used[10]. When we consider the utilization observed in Saskatchewan, the cost of running a machine for 1 year is $48,546.

Figure 20: Budget Impact Analysis of Costs per Various Numbers of Sessions

Initial Investment (excluding space)	Machine + Chair +Nurse $85,000 + $500 + $90,000/year ($45.03/hour) = $175,500				
	Current Alberta Utilization		**Current NICE Utilization**		**Current Saskatchewan Utilization**
Capacity	*100%*	*70%*	*100%*	*70%*	*100%*
Sessions per year	408	286	348	244	1,497
Cost per session (Machine and Staff)	$48	$56	$51	$62	$32
Cost per 20 sessions / 1 Treatment Course	$952	$1,129	$1,024	$1,232	$649
Cost of running 1 machine for 1 year	$19,415	$16,151	$17,809	$15,027	$48,546

6.5 Discussion

rTMS is more costly and more effective than sham at achieving response and remission with a cost per QALY gained of $13,084 and $20,203, respectively. When comparing rTMS to ECT, rTMS is more effective and less costly than ECT when considering response. ECT is associated with a cost per QALY gained of $328,325 compared to rTMS when remission is modeled.

Uncertainty in the cost per QALY estimates is mainly due to uncertainty in the relative risks estimates of rTMS for both response and remission. When varied within the 95% CI, the cost per QALY varies greatly, although when compared to sham, the 95% CI does not include 1.00; thus when modeled, rTMS is always more effective and more expensive than sham. However, compared to ECT, when the lower 95% CI for remission is modeled, rTMS becomes the less effective, more expensive option. The threshold costs of rTMS compared to ECT or standard therapy demonstrate that the costs needed to make rTMS the least cost-effective option are over twice the predicted costs, which may not necessarily be what would ever be seen in a real-life scenario. Considering the overall uncertainty with the PSA the large majority of the time rTMS is more cost-effective than either standard therapy or ECT for both response and remission.

The informal care costs were not taken into account with any of these models. A scenario analysis was performed on the response and remission models comparing rTMS and ECT including the 6-month follow-up costs. With inclusion of the informal costs, rTMS was still more cost-effective even though the predicted follow-up costs for rTMS were substantially higher than ECT. However, the cost estimates were based on a UK-based study and the costs may not be directly transferable to the Canadian context.

Our models only consider the short-term outcomes of response and remission (approximately 4-6 weeks). There is insufficient data available to model the impact of rTMS on longer term outcomes such as relapse or reoccurrence, serious events (suicide attempt, hospitalization) or, arguably, the most meaningful outcomes such

as return to work or ability to complete daily tasks. The understanding of the economic impact of rTMS is hampered without these types of outcomes.

6.6 Conclusions

rTMS is more costly and more effective than sham at achieving response and remission with a cost per QALY gained of $13,084 and $20,203, respectively. Comparing rTMS to ECT, rTMS is more effective and less costly than ECT the majority of the time. The estimated budget impact remains unknown as no reliable estimate of demand was possible. However, the total fixed investment is $175,500. The marginal cost for the first session is $132.33 and the marginal cost for ongoing sessions is $47.60 (accounting for 15 minutes of nursing time). Additional data on the long-term impact of rTMS is required to support more in-depth modeling.

7 Systematic Review of rTMS for Treatment Resistant Youth and Young Adults with Unipolar or Bipolar Depression

Summary of Effectiveness findings for Youth:

- *Three studies reporting on two populations were included in this systematic review of rTMS for youth and young adults with treatment resistant depression*
- *The included studies suggest that rTMS may be an effective intervention for treatment resistant youth and young adults, however, the evidence is too weak to be able to draw conclusions*
- *Additional literature on the use of rTMS to treat youth and young adults with treatment resistant depression is required in order to draw conclusions about efficacy or effectiveness*

7.1 Introduction

The World Health Organization defines health as "…a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." Mental health is an integral part of an individual's overall health and wellbeing, and has a significant personal, social and economic impact on Canadians. The Canadian Mental Health Association reports that 20% of all Canadians will experience a mental illness in their lifetime[134]. The youth and young adults of Canada are similarly vulnerable to the impact of mental illness. It has been estimated that in Canada, 5% of males and 12% of females ages 12-19 have been diagnosed with a major depressive episode, and that 3.2 million are at risk of developing depression[134].

Depression in youth (13-17 years old) and young adults (18-25 years old) may result in symptoms such as decreased interest in activities, withdrawal from friends, change in appetite, change in sleep patterns, fatigue, decrease in energy, suicidal ideation or self-destructive behaviour, feelings of sadness, irritability, tearfulness, and difficulty concentrating[135]. Tools for measuring depression severity in youth and young adults include, but are not limited to, the Children's Depression Rating Scale[136], the Children's Depression Inventory[137], the Beck Youth Inventories[138], and the Center for Epidemiological Studies-Depression Scale for Children[139].

In youth and young adults, various treatment options are available including psychotherapy, pharmaceuticals, and cognitive behavioural therapy[20;140;141]. Pharmaceutical treatment options, approved by Health Canada for use with youth and young adults include Citalopram, Fluoxetine, Fluvoxamine, Mirtazapine, Paroxetine,

Sertraline and Venlafaxine[142]. Although a variety of treatment options are available to youth and young adults with depression, some patients do not experience adequate improvement using the above mentioned treatment options.

For treatment resistant youth, ECT is currently the primary treatment option. Although ECT is used to treat youth, it is not optimal due to the possibility of severe side effects such as cognitive impairment[143]. Repetitive Transcranial Magnetic Stimulation (rTMS), an emerging therapy which generates a magnetic field in order to influence cerebral electric activity (see section **Error! Reference source not found.** for a more complete description of the technology), may be an alternative treatment option to ECT for youth and young adults who are treatment resistant. The purpose of this systematic review is to synthesize the current peer-reviewed literature addressing the use of rTMS for youth and young adults with TRD.

7.2 Methods

A systematic review was completed. MEDLINE, the Cochrane CENTAL Register of Controlled Trials, PubMED, EMBASE, PsychINFO, the Cochrane Database of Systematic Reviews and the HTA Health Technology Assessment Database, were searched from inception until January 10th, 2014. Terms aimed at capturing the target diagnosis, such as "Depressive Disorder," "bipolar disorder" and "depression" were combined using the Boolean Operator "or." Using the Boolean Operator "and", these terms were combined with terms used to describe the technology, such "rtms," "tms" and "transcranial magnetic stimulation." Results were limited to humans, excluded editorials and letters, and were limited by age to include only youth (13-17 years of age) or young adults (18-25 years of age). No other limitations were used. Details of this search are available in **Appendix D**.

All abstracts identified were screened in duplicate (LL and SC). Articles proceeded to full text review if the study included only treatment resistant participants, between the ages of 12-25, with a diagnosis of uni- or bi-polar depression, and if the study reported on the effectiveness of rTMS. Abstracts were excluded if they did not meet the inclusion criteria above or if the study did not report original data or included animals, data was only available as an abstract or poster, and/or case study or case series design was used. Abstracts selected for

inclusion by either reviewer proceeded to full-text review. This initial screen was intentionally broad to ensure that all relevant literature was captured.

Studies included after abstract review proceeded to full-text review in duplicate (LL and SC). Studies were included if they met all inclusion criteria and failed to meet any of the criteria for exclusion presented in **Table 24**. Any discrepancy between reviewers was resolved through consensus. A kappa statistic for reviewer agreement was calculated.

Table 24 Inclusion/Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
▪ Report TRD or report patients have had 2+ previous treatments ▪ Youth and young adult (12-25 years) population ▪ Report on one of the following: o Effectiveness of rTMS in comparison to placebo, pharmacological therapy, cognitive therapy or ECT o Effectiveness of one type/protocol of rTMS treatment in comparison to another type/protocol of rTMS treatment ▪ Bipolar or unipolar depression ▪ Patients who have not been treated with rTMS prior to study ▪ Include controlled clinical trials, RCTs, cohort studies	▪ Not TRD or do not report whether patients have TRD ▪ Non-original data ▪ Not rTMS ▪ Not unipolar or bipolar depression ▪ Animal models ▪ Preclinical and biological studies ▪ Studies reported only in abstract or as poster presentations ▪ Not reporting on efficacy of rTMS ▪ Studies including patients who have not responded to rTMS in previous treatments ▪ Case studies, case series

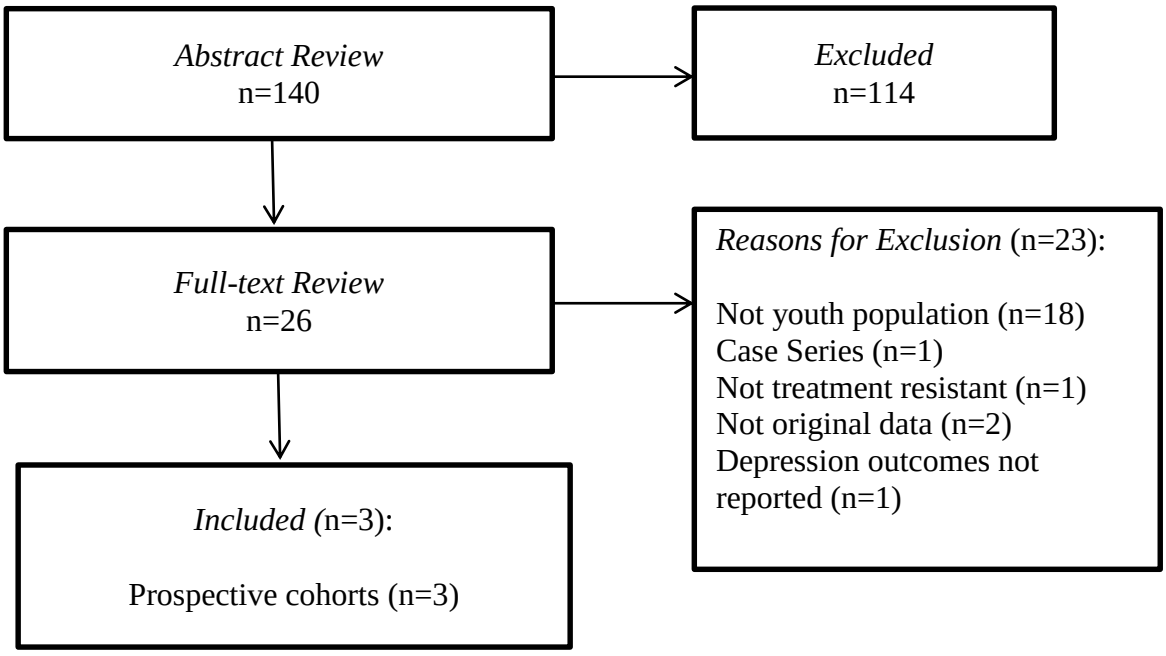
Study characteristics, such as date of publication, patient selection, comparators and outcome measures, and study results were extracted in duplicate (LL and LS). Discrepancies between reviewers during data extraction were resolved through consensus.

Quality of each study was assessed based on the Downs and Black Checklist[144]. Assessment was completed in duplicate (LS and LL) with discrepancies being resolved through discussion. Using this scale, each study is assessed based on 27 criteria, widely covering areas reporting quality, external and internal validity, and power[144]. Studies are assigned a value of "1" if they meet the question criteria, "0" if they do not or if it is not possible to determine, with one exception where one question may be given "2" points[144]

7.3 Results

The literature search identified 140 abstracts. Of these, 114 were excluded after abstract review, and 26 proceeded to full-text review. After full-text review, twenty three papers were excluded due to various reasons: not a youth population (n=18), case series design (n=1), included participants who were not treatment resistant (n=1), did not report original data (n=1), and did not report outcomes on change in depression severity (n=1). Ultimately, three papers were included in this systematic review (Kappa: 0.63, 95% CI: 0.169-1.00; see **Figure 21**). These three papers report on two patient populations. Two of the included papers report on the same patient population; one reports short-term outcomes[145] and the other reports long-term outcomes[146].The limited number of included studies, and heterogeneous nature of the outcomes reported did not permit meta-analysis. Therefore, the results from each study are narratively summarized below.

Figure 21: Flow chart of Studies Included and Excluded during Systematic Review of rTMS for Treatment Resistant Youth and Young Adults with Depression



7.3.1 Study Characteristics

Characteristics of each included study have been summarized in **Table 25**. These studies were conducted in Israel[145], the United States[147] and Australia[146], and all three were designed as prospective cohort studies. Studies

were conducted between 2008[145] and 2012[146;147]. All three studies were small including 7[146;147] to 9[145] participants. Mayer et al.[146] recruited participants from a previously conducted open-label trial and reported patients' long-term outcomes (6 years post-treatment) based on their treatment in the earlier trial. Bloch et al.[145] and Croarkin et al.[147], recruited participants from medical centers and reported short-term outcomes after rTMS treatment (1 month post-treatment and 5 weeks post treatment, respectively).

Table 25: Characteristics of Studies Included in Systematic Review of rTMS for Treatment Resistant Youth and Adolescents with Depression

Author, Year of Publication, Country	*Patient Selection*	*Exposure*	*Outcomes*
Bloch[145], 2008, Israel	**Patient Selection:** Participants were recruited from 1 inpatient adolescent ward and 1 outpatient clinic **Inclusion Criteria:** Age 16-18, diagnosis of major depression as defined by DSM-IV **Exclusion Criteria:** Schizophrenia, bipolar disorder, substance abuse, psychosis, history of epilepsy, any other neurological disorder **Patient Characteristics:** Nine participants were included (7 females, 2 males) with a mean age of 17.3 years **Definition of Treatment Resistance:** Failure of one trial of psychotherapy, and two courses of medications for 8 weeks each, at least one with fluoxetine	**rTMS:** 10 Hz rTMS stimulation to the left dorsolateral prefrontal cortex at 80% motor threshold for 14 sessions over 14 days	**Outcomes measured:** Child Depression Rating Scale, Child Anxiety Related Disorder screen, Suicide Ideation Questionnaire, Clinical Global Impression scale, Cambridge Neuropsychological Test Automated Battery **Follow-up time:** 6 weeks **Outcome ascertainment:** Baseline, day 7 and 10 of therapy, end of therapy, and 1 month post-therapy
Croarkin[147], 2012, United States	**Patient Selection:** Participants were recruited from 2 inpatient treatment centers **Inclusion Criteria:** stable therapy within prior 4 weeks **Exclusion Criteria:** Schizophrenia, Schizoaffective disorder, bipolar spectrum disorder, substance abuse/dependence, somatoform disorder, dissociative disorder, post-traumatic stress disorder, obsessive-compulsive disorder, eating disorder, mental retardation, pervasive developmental disorder, pregnancy, ongoing treatment with stimulants, antipsychotics, mood-stabilizers or non-serotonin-selective reuptake inhibitors **Patient Characteristics:** Seven participants (6 females, 1 male), with a mean age of 16.5, were included. **Definition of Treatment Resistance:** Failure to respond to at least two adequate antidepressants	**rTMS:** 10 Hz rTMS stimulation to the left dorsolateral prefrontal cortex at 120% motor threshold for 30 sessions within 6-8 weeks	**Outcomes measured:** Children's Depressive Rating Scale-Revised, Quick Inventory of Depressive Symptomatology **Follow-up time:** Five weeks **Outcome ascertainment:** Baseline, and weeks 2,4,5
Mayer[146], 2012, Australia	**Patient Selection:** Participants were recruited from a previously conducted open-label trial on rTMS conducted in 2006. **Inclusion Criteria:** Received treatment in 2006 study, consented to follow-up **Exclusion Criteria:** None reported **Patient Characteristics:** Eight participants (6 females, 2 males) with a mean age of 20.4 were included. All participants received rTMS in original 2006 study **Definition of Treatment Resistance:** Not reported	**rTMS:** Provided in 2008 study by Bloch et al.[145]	**Outcomes measured:** Beck Depression Inventory Version II, Children's Depression Rating Scale-Revised, Cambridge Neuropsychological Test Automated Battery **Outcome ascertainment:** Three years post-treatment

Mayer et al.[148] provide long-term outcomes of the patients in the study by Bloch et al.[145]; they did not provide new rTMS treatment beyond that given in the study by Bloch et al. Therefore, the rTMS protocols in Mayer et al. and Bloch et al. are one in the same. Bloch et al. used 10 Hz rTMS at 80% motor threshold for 14 sessions[145]. Croarkin et al. used 10 Hz rTMS at 120% motor threshold for 30 sessions over a period of 6-8 weeks[149]. All three studies targeted the left dorsolateral prefrontal cortex. The definition of treatment resistance also varied among the included studies. Bloch et al. defined treatment resistance as failure to respond to one trial of psychotherapy and two courses of medication for 8 weeks each (one being fluoxetine)[145]. Croarkin et al. defined treatment resistance as a failure to respond to at least two adequate trials of antidepressants[147].

Outcomes reported across all studies included the Children's Depression Rating Scale[145-147], the Cambridge Neuropsychological Test Automated Battery[145;146], Child Anxiety Related Disorders screen[145], Suicide Ideation Questionnaire[145], Clinical Global Impression Scale[145], Quick Inventory of Depressive Symptomatology[147] and the BDI (Version II)[146].

7.3.2 Quality Assessment of Included Studies

Quality assessment scores for these studies ranged from 15 to 17 out of a total possible 23 points (**Table 26**). Although usually scored out of 28, a modified Downs and Black Checklist was used since the included studies assessed one intervention with no comparator; thereby reducing the denominator to 23. The areas where quality was most often lacking was whether an attempt was made to blind study subjects or those measuring intervention outcomes, respectively (questions 14 and 15).

Table 26: Quality Assessment of Included studies, as Assessed by the Downs and Black Checklist

	Bloch[145]	**Croarkin**[147]	**Mayer**[146]
Question 1	1	1	1
Question 2	1	1	1
Question 3	1	1	1
Question 4	1	1	1
Question 5	1	1	1
Question 6	1	1	1
Question 7	0	1	0
Question 8	1	0	1
Question 9	1	0	Unable to Determine
Question 10	0	1	0
Question 11	Unable to Determine	Unable to Determine	Unable to Determine
Question 12	Unable to Determine	Unable to Determine	Unable to Determine
Question 13	1	1	1
Question 14	0	0	0
Question 15	0	0	0
Question 16	1	1	1
Question 17	1	1	1
Question 18	1	1	1
Question 19	1	1	1
Question 20	1	1	1
Question 21	Not applicable	Not applicable	Not applicable
Question 22	Not applicable	Not applicable	Not applicable
Question 23	Not applicable	Not applicable	Not applicable
Question 24	Not applicable	Not applicable	Not applicable
Question 25	1	Unable to Determine	Unable to Determine
Question 26	1	1	1
Question 27	1	1	1
Total	**17**	**16**	**15**

7.3.3 Effectiveness of Repetitive Transcranial Magnetic Stimulation

Bloch et al. assessed the effectiveness of rTMS at baseline, day 7, 10, 14, and 1 month post-treatment[145]. At 1 month post-treatment, 3 out of nine participants experienced clinical response (at least a 30% reduction in the Child Depression Rating Scale)[145]. This study also found statistically significant reductions in depression measured using the BDI at days 7, 10 and 1 month post-treatment, when compared to baseline ($p<0.05$)[145]. Using the Screen for Child Anxiety-Related Disorders Questionnaire, participants' anxiety levels were significantly lower at the end of treatment and one month post-treatment ($p<0.05$) [145]. Statistically significant results were not found with the Suicide Ideation Questionnaire at any time point, suggesting that there is no evidence to suggest that rTMS has an effect on suicidal ideations and behaviours[145].

Mayer et al. reported long-term (3 year) outcomes of participants who had originally taken part in the study above[150]. Mayer et al. found no statistically significant differences in long-term follow-up outcomes when compared to outcomes at the end of treatment. This suggests that participants experienced initial improvement in their depression severity, and did not experience ant statistically significant changes (either worsening or improvement) in depression severity between the time of treatment and time of 3 year follow-up[146].

Croarkin et al. assessed outcome measures at baseline, weeks, 2, 4 and 6. Clinical response and remission were not reported. However, the mean Child Depression Rating Scale score was reduced from 69.3 (8.6) at baseline to 42.1(10.7) (average of week 2, 4, and 6 outcomes reported). This study also reported increases in cortical activity over time when baseline is compared to week five.

7.3.4 Safety

Only one of the included studies, Bloch et al. reported adverse events related to rTMS treatment. This study reports that 5 out of 9 participants experienced a headache in response to rTMS treatment[145]. No other adverse events were reported by participants[145].

7.4 Discussion

This section reviews the effectiveness of rTMS for the treatment of TRD in youth and adolescents from age 12-25. The three included papers describe change in depression severity in individuals treated with rTMS.

Compared to the breadth of adult literature available on the use of rTMS to treat depression, there is very little literature on youth and adolescent populations.

Using the Children's Depression Rating Scale, both of the studies assessing short-term outcomes found a reduction in depression severity after rTMS treatment; one reported statistically significant reductions[145] while the other did not conduct tests of significance[147]. The study that reported significance found statistically significant reductions in depression severity at day 7, 10 and 1 month post-treatment[145]. Other outcome measures such as the BDI[145;146], and the Screen for Child Anxiety Related Disorders Questionnaire[145] also suggested statistically significant reduction in depression severity.

The results from the three included papers suggest that that rTMS may be an effective method of alleviating severe depression in youth and young adults who have failed to respond to other methods of treatment. However, the limited number and the low to moderate quality of the studies on this topic limit the ability to draw generalized conclusions about the use of rTMS with this population. The rTMS protocols were heterogeneous among the included studies, precluding inference of the most appropriate protocol for this patient population. Furthermore, the small sample size in each paper, with a total of twenty-five participants included in all three studies, does not provide a robust evidence base.

With depression affecting a sizeable number of youth and adolescents, finding acceptable, efficacious treatments for this patient population is of particular importance. The included literature suggests that rTMS may be an effective treatment option for youth and young adults with depression. However, with limited literature and data available, further studies, particularly large-scale high quality studies with this patient population, are required before conclusive inferences can be drawn.

7.5 Conclusion

The literature on this topic is weak. The included studies suggest that rTMS may be an effective intervention for treatment resistant youth and young adults; however, the evidence is too weak to be able to draw conclusions.

Additional literature on the use of rTMS to treat youth and young adults with TRD is required in order to draw conclusions about efficacy or effectiveness.

8 Limitations

This HTA has several limitations that merit comment, including the heterogeneity of literature, lack of literature, and the use of surrogate outcomes.

As with all systematic reviews, this research is limited by the literature available. In the adult review of efficacy, the procedure protocols were heterogeneous (e.g. various frequencies, motor thresholds, number of sessions). Although studies were divided by comparator, it was not possible to further divide them based on small protocol differences. As no statistically significant differences were found between protocol differences such as high and low frequency, unilateral and bilateral treatment and high and low intensity, it is unlikely that pooling these protocols would have introduced significant bias.

The youth review was limited by the number of studies available. There are few studies conducted on the use of rTMS for youth with TRD, and as a result, it was not possible to draw conclusions about effectiveness. Additional research on this topic is required before robust conclusions can be drawn.

Treatment response and remission were the primary outcomes assessed. These outcomes were used because they are frequently reported, and give a broad sense of patient improvement or worsening. Ideally, outcomes such as function and quality of life would be the primary outcomes assessed, as these outcomes would more closely determine the impact of rTMS treatment on a patient's life. However, measures of function and/or quality of life are not frequently found in the literature; not enough data exists to pool. A major limitation is that the outcomes available in the literature are not directly measuring improvement in patient quality of life.

Both of the systematic reviews on effectiveness/efficacy and safety of rTMS (adult and youth) were limited by a lack of studies reporting long-term data. The vast majority of studies on rTMS assess only the short-term impact of treatment (4-6 weeks). Due to limited long-term data, it is not possible to draw conclusions about the length of treatment effect, the long-term safety of treatment, and the impact of treatment on outcomes such as return to

work or ability to complete daily tasks. Studies reporting long-term patient outcomes, such as relapse, reoccurrence, participation in life and major side effects are required.

9 Conclusions

Key informants feel that rTMS should be considered as one treatment option as part of the overall care pathway for patients with MDD and TRD. rTMS is currently being provided to adults with TRD at two locations in Alberta, the Centennial Centre in Ponoka (funded publicly) and the Riverview Medical Clinic in Calgary (funded privately) resulting in inequitable access within the province. rTMS is available to youth and young adults in the context of research through the Alberta Children's Hospital. For adults, rTMS is twice as effective as sham at achieving both response (RR 2.35 95% CI 1.70-3.25) and remission (RR: 2.24 95% CI 1.53-3.27). Compared to ECT, the performance of rTMS is unclear with no statistical difference between response (RR: 1.09 (95% CI: 0.79-1.48) and remission (RR: 1.09 (95% CI: 0.79-1.48) between the two treatments. Minor adverse events, such as headache and discomfort, are equivalent between the treatments. All the data reported are short-term (4-6 weeks) with no data supporting relapse rates, reoccurrence, major adverse events or ability to complete daily tasks.

The cost per QALY gained with rTMS compared to sham is $13,084 for response and $20,203 for remission. Comparing rTMS to ECT, rTMS is more effective and less costly than ECT the majority of the time. The estimated budget impact remains unknown, as no reliable estimate of demand was possible. However, the total fixed investment required for 1 rTMS machine is $85,000 and the estimated marginal cost per procedure is $22.52. The economic model is limited by the lack of clinical data reporting long-term outcomes.

Little literature exists assessing youth and young adults. From the 3 identified studies, rTMS appears to be a promising treatment; however, a RCT in this population has yet to be completed to establish the effectiveness of rTMS. Future work should focus on establishing the optimal rTMS protocol, the long-term effect of rTMS and the effectiveness of rTMS in the youth and young adult population.

10 Appendix A: Mental Health Service Delivery in Northern Alberta

MH services in Grand Prairie

The hospital in Grand Prairie has 14 designated mental health beds, and 2 overcapacity beds. All 16 beds are almost always occupied.

They have ECT equipment at the hospital in Grand Prairie but only one psychiatrist uses it. He provides ECT treatments twice a week. He's been doing this since about 2006 2007. This is primarily done on an inpatient basis but he will also occasionally treat people as outpatients.

Concern about the future, as this particular psychiatrist will be retiring sometime in the next few years. Hoping that one of the new psychiatrists will pick up the ECT treatments.

A large percentage of the patients getting ECT treatments are seniors. Sometimes seniors requiring ECT treatment can be admitted to the short-term dementia unit (i.e., rather than having to wait for one of the 16 mental health beds to become available).

Access to ECT is particularly difficult for people living in outlying areas, because they need to be admitted as an inpatient for about six weeks [assuming that this is for the original course of treatment]. Even if patients are willing to come in for ECT treatment, bed capacity issue affect access.

There are currently four adult psychiatrists practicing in Grand Prairie, with a new one starting in November. Of these, three will be hospital-based psychiatrists and two will be community-based.

They have also had one child psychiatrist practicing there since February 2013.

Regarding turnover of psychiatrists, things have been pretty stable since about 2007. Between 2005-2007 all of the psychiatrists left. Two of the current psychiatrists have been there since 2006-2007 and another since 2008.

There is also a day treatment program in Grand Prairie and cognitive behavioral therapy is a big part of that program.

Have moved from four days of treatment per week to 2 group treatments per week, in an effort to increase access to treatment.

All therapists will do some cognitive behavioural therapy. Some might do a combination of treatments, with the treatment preferences usually influenced by their training. Most of their therapists are psychologists. Even therapists practicing in rural areas would all currently provide at least some Cognitive behavioural therapy.

MH services in other centres in the North:

Fort McMurray hospital has a 10-bed inpatient mental health unit. They also have four adult psychiatrists. There is no access to ECT (no ECT equipment).

St. Paul has two adult psychiatrists. This is a small rural community so their acuity is not as high. No ECT is done there either.

There is a .6 FTE psychiatrist based in Peace River, in the community.

11 Appendix B: Search Strategy for Review on Patient Experiences with rTMS

MEDLINE (OVID)
1. Transcranial Magnetic Stimulation/
2. (transcranial adj2 magnetic adj2 stimulation*).tw.
3. (rtms or tms magnetic seizure therap* or mst).tw.
4. 1 or 2 or 3
5. exp Depressive Disorder/
6. (depression* or depressed or depressive).tw.
7. 5 or 6
8. 4 and 7
9. limit 8 to animals
10. limit 8 to (animals and humans)
11. 9 not 10
12. 8 not 11
13. limit 12 to english language
14. qualitative research/
15. interviews as topic/ or focus groups/
16. interview/
17. grounded theory.tw.
18. (interview* or focus group* or qualitative).tw.
19. (attitude* or beliefs or experiences or perception* or preference*).tw.
20. lived experience*.tw.
21. exp Attitude to Health/
22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 13 and 22

EMBASE (OVID)
1. transcranial magnetic stimulation/
2. (transcranial adj2 magnetic adj2 stimulation*).tw.
3. (rtms or tms or magnetic seizure therap* or mst).tw.
4. 1 or 2 or 3
5. exp depression/
6. (depression* or depressed or depressive).tw.
7. 5 or 6
8. 4 and 7
9. limit 8 to animals
10. limit 8 to (human and animals)
11. 9 not 10
12. 8 not 11
13. limit 12 to english language
14. qualitative research/
15. qualitative analysis/

16. exp interview/
17. grounded theory/
18. personal experience/
19. attitude/ or attitude to health/ or attitude to illness/ or attitude to mental illness/ or exp patient attitude/
20. (interview* or focus group* or grounded theory or qualitative).tw.
21. (attitude* or beliefs or experiences or perception* or preference*).tw.
22. lived experience*.tw.
23. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 13 and 23

PsycINFO (OVID)
1. transcranial magnetic stimulation/
2. (transcranial adj2 magnetic adj2 stimulation*).tw.
3. (rtms or tms or magnetic seizure therap* or mst).tw.
4. 1 or 2 or 3
5. exp major depression/
6. (depression or depressive or depressed).tw.
7. 5 or 6
8. 4 and 7
9. limit 8 to animal
10. limit 8 to (animal and human)
11. 9 not 10
12. 8 not 11
13. limit 12 to english language
14. limit 13 to ("0700 interview" or "0750 focus group" or 1600 qualitative study)
15. qualitative research/ or grounded theory/ or exp interviews/
16. observation methods/
17. group discussion/
18. life experiences/
19. attitudes/ or health attitudes/
20. client attitudes/
21. (interview* or focus group* or grounded theory or qualitative or lived experience*).tw.
22. (attitude* or beliefs or experiences or perception* or preference*).tw.
23. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 13 and 23
25. 14 or 24

CINAHL (EBSCO)

1. magnet therapy[MH]
2. (transcranial N2 magnetic N2 stimulation*)[Title/Abstract]
3. (rtms or tms or magnetic seizure therap* or mst)[Title/Abstract]
4. 1 or 2 or 3
5. depression+[MH]
6. (depression or depressive or depressed)[Title/Abstract]
7. 5 or 6
8. 4 and 7
9. Limit 8 to English language
10. (qualitative studies+ or observational methods or focus groups or interviews or semi-structured interview or life histories or life experiences or attitude or attitude to health or patient satisfaction)[MH]
11. (interview* or focus group* or grounded theory or qualitative or lived experience*)[Title/Abstract]
12. (attitude* or beliefs or experiences or perception* or preference*)[Title/Abstract]
13. 10 or 11 or 12
14. 9 and 13

12 Appendix C: Search Strategy for Systematic Review of Adult Literature

MEDLINE (OVID)
1. Depressive Disorder, Major/
2. bipolar disorder/ or cyclothymic disorder/
3. (depression or depressive disorder).tw.
4. 1 or 2 or 3
5. rtms.tw.
6. tms.tw.
7. (transcranial adj3 magnetic adj3 stimulation*).tw.
8. Transcranial Magnetic Stimulation/
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to animals
12. limit 10 to (animals and humans)
13. 11 not 12
14. 10 not 13
15. limit 14 to (editorial or letter)
16. 14 not 15
17. (randomized controlled trial or controlled clinical trial).pt.
18. drug therapy.sh.
19. (groups or placebo or randomized or randomly or trial).tw.
20. 17 or 18 or 19
21. 16 and 20

Cochrane CENTRAL Register of Controlled Trials (OVID)
1. Depressive Disorder, Major/
2. bipolar disorder/ or cyclothymic disorder/
3. (depression or depressive disorder).tw.
4. 1 or 2 or 3
5. rtms.tw.
6. tms.tw.
7. (transcranial adj3 magnetic adj3 stimulation*).tw.
8. Transcranial Magnetic Stimulation/
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to animals
12. limit 10 to (animals and humans)
13. 11 not 12
14. 10 not 13
15. limit 14 to (editorial or letter)
16. 14 not 15

PubMED
1. Depressive Disorder, Major[MeSH] or bipolar disorder[MeSH]
2. (depression or depressive disorder)[tiab]
3. 1 or 2
4. rtms[tiab] or tms[tiab]
5. transcranial magnetic stimulation[MeSH]
6. (transcranial magnetic stimulation*)[tiab]
7. 4 or 5 or 6
8. 3 and 7
9. limit 8 to animals
10. limit 8 to (animals and humans)
11. 9 not 10
12. 8 not 11
13. limit 12 to (editorial or letter)
14. 12 not 13
15. limit to (randomized controlled trial or controlled clinical trial)[Publication Type].

EMBASE (OVID)
1. major depression/
2. (depression or depressive disorder).tw.
3. bipolar depression/
4. 1 or 2 or 3
5. transcranial magnetic stimulation/
6. (transcranial adj3 magnetic adj3 stimulation*).tw.
7. rtms.tw.
8. tms.tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to animal studies
12. limit 10 to (human and animal studies)
13. 11 not 12
14. 10 not 13
15. limit 14 to (conference abstract or editorial or letter)
16. 14 not 15
17. Randomized Controlled Trial/
18. Single Blind Procedure/
19. crossover procedure/
20. double blind procedure/
21. (allocat* or assign* or crossover* or cross over* or (doubl* adj blind*) or factorial* or placebo* or random* or (singl* adj blind*) or volunteer*).tw.
22. 17 or 18 or 19 or 20 or 21
23. 16 and 22

PsycINFO (OVID)
1. exp Major Depression/
2. (depression or depressive disorder*).tw.
3. bipolar disorder/
4. 1 or 2 or 3
5. exp Transcranial Magnetic Stimulation/
6. (transcranial adj3 magnetic adj3 stimulation*).tw.
7. (tms or rtms).tw.
8. 5 or 6 or 7
9. 4 and 8
10. clinical trials/
11. (allocat* or assign* or crossover* or cross over* or (doubl* adj blind*) or factorial* or placebo* or random* or (singl* adj blind*) or volunteer*).tw.
12. 10 or 11
13. 9 and 12

Cochrane Database of Systematic Reviews (OVID)
HTA Health Technology Assessment Database (OVID)
1. (depression or depressive disorder).tw.
2. rtms.tw.
3. tms.tw.
4. (transcranial adj3 magnetic adj3 stimulation*).tw.
5. 2 or 3 or 4
6. 1 and 5

13 Appendix D: Search Strategy for Systematic Review on the Effectiveness of rTMS for Treatment Resistant Youth and Adolescents with Uni- or Bi-polar Depression

MEDLINE (OVID)
Cochrane CENTRAL Register of Controlled Trials (OVID)
1. Depressive Disorder, Major/
2. bipolar disorder/ or cyclothymic disorder/
3. (depression or depressive disorder).tw.
4. 1 or 2 or 3
5. rtms.tw.
6. tms.tw.
7. (transcranial adj3 magnetic adj3 stimulation*).tw.
8. Transcranial Magnetic Stimulation/
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to animals
12. limit 10 to (animals and humans)
13. 11 not 12
14. 10 not 13
15. limit 14 to (editorial or letter)
16. 14 not 15
17. limit 16 to "all child (0 to 18 years)"
18. (child* or adolescen* or infant* or pediatric* or paediatric*).tw.
19. 16 and 18
20. 17 or 19

PubMED
1. Depressive Disorder, Major[MeSH] or bipolar disorder[MeSH]
2. (depression or depressive disorder)[tiab]
3. 1 or 2
4. rtms[tiab] or tms[tiab]
5. transcranial magnetic stimulation[MeSH]
6. (transcranial magnetic stimulation*)[tiab]
7. 4 or 5 or 6
8. 3 and 7
9. limit 8 to animals
10. limit 8 to (animals and humans)
11. 9 not 10
12. 8 not 11
13. limit 12 to (editorial or letter)

14. 12 not 13
15. (child* or adolescen* or infant* or pediatric* or paediatric*)[tiab]
16. 14 and 15

EMBASE (OVID)
1. major depression/
2. (depression or depressive disorder).tw.
3. bipolar depression/
4. 1 or 2 or 3
5. transcranial magnetic stimulation/
6. (transcranial adj3 magnetic adj3 stimulation*).tw.
7. rtms.tw.
8. tms.tw.
9. 5 or 6 or 7 or 8
10. 4 and 9
11. limit 10 to animal studies
12. limit 10 to (human and animal studies)
13. 11 not 12
14. 10 not 13
15. limit 14 to yr="1989 -Current"
16. limit 15 to (conference abstract or editorial or letter)
17. 15 not 16
18. limit 17 to (infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
19. (child* or adolescen* or infant* or pediatric* or paediatric*).tw.
20. 17 and 19
21. 18 or 20

PsycINFO (OVID)
1. exp Major Depression/
2. (depression or depressive disorder*).tw.
3. bipolar disorder/
4. 1 or 2 or 3
5. exp Transcranial Magnetic Stimulation/
6. (transcranial adj3 magnetic adj3 stimulation*).tw.
7. (tms or rtms).tw.
8. 5 or 6 or 7
9. 4 and 8
10. limit 9 to (100 childhood or 120 neonatal or 140 infancy <2 to 23 mo> or 160 preschool age or 180 school age or 200 adolescence)
11. (child* or adolescen* or infant* or pediatric* or paediatric*).tw.
12. 9 and 11
13. 10 or 12

Cochrane Database of Systematic Reviews (OVID)
HTA Health Technology Assessment Database (OVID)
1. (depression or depressive disorder).tw.
2. rtms.tw.
3. tms.tw.
4. (transcranial adj3 magnetic adj3 stimulation*).tw.
5. 2 or 3 or 4
6. 1 and 5

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