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Evidence Check

Transcranial Magnetic Stimulation for Major Depression and Schizophrenia

An **Evidence Check** rapid review brokered by the Sax Institute for the NSW Ministry of Health. August 2017

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Suggested Citation:

Ma N, Atukorale Y, Marlow N, Duncan J, Cameron A (2017) Transcranial Magnetic Stimulation for major depression and schizophrenia: an Evidence Check brokered by the Sax Institute (www.saxinstitute.org.au) for the NSW Ministry of Health, 2017.

Transcranial Magnetic Stimulation for Major Depression and Schizophrenia

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August 2017.
This report was prepared by Ning Ma, Yasoba Atukorale, Joanna Duncan, Nicholas Marlow, Alun Cameron.

Contents

Glossary of terms

Bipolar disorder[1, 2]

Bipolar disorder is characterised by the presence of at least one manic or mixed (manic and depressive features) episode or by the presence of at least one major depressive episode with at least one hypomanic episode. In this report, the term bipolar disorder is used to refer to bipolar disorder where Transcranial Magnetic Stimulation (TMS) has been investigated as a treatment for major depressive symptoms.

Major depression[3]

Major depression is characterised by the presence of symptoms including: depressed mood; diminished interest or pleasure in activities; changes to weight, sleep or energy levels; feelings of worthlessness or guilt; diminished cognitive function; and, recurrent thoughts of death where the symptoms cannot be attributed to another medical condition. The severity of the depressive episode is based on the number of symptoms present, the severity of the symptoms and the degree of functional disability. This definition reflects that of DSM V and ICD 10. Major depression may also be referred to as major depressive disorder, clinical depression or unipolar depression.

Motor threshold[4]

The motor threshold is the minimum intensity of magnetic field required to elicit a motor response in the patient. The motor threshold for an individual varies due to a number of factors (physiological, type of machine) and allows the intensity of the TMS to be modified to correct variance.

Schizophrenia[5]

Schizophrenia is characterised by the presence of symptoms which can be grouped into the following categories: positive symptoms (hallucinations, paranoid delusions, distorted perceptions); negative symptoms (decrease in ability to speak, express emotion or find pleasure); and cognitive symptoms (problems with attention, memory, performance). For a diagnosis of schizophrenia at least two symptoms must be present for at least one month, one of which must be hallucinations, delusions or disorganised speech. This definition is based on that of DSM V and ICD 10.

Sham

Sham TMS is designed to mimic active TMS therapy in sound (and sensation) without eliciting intracortical activity. This may be achieved by tilting the magnetic coil angled off the scalp or using a sham coil which mimics the sounds of active TMS. If any co-interventions (e.g. pharmaceuticals) are used in the active TMS arm of the study then these would also be used in the same way in the sham arm. The use of co-interventions depends on individual Randomised Control Trials (RCTs).

Standard care

Standard care describes the use of pharmaceuticals (antidepressants with or without other medications) for the treatment of major depression. Standard care does not include minimally invasive procedures such as Electroconvulsive Therapy (ECT). Each study may have used a different combination of treatments depending on their definition of what constitutes standard care.

Transcranial magnetic stimulation (TMS)[6, 7]

Transcranial magnetic stimulation involves the generation of magnetic fields near the scalp to induce electrical currents in the brain. TMS can be applied as a single pulse, as two pulses (paired TMS) or as a series of pulses (repetitive TMS or rTMS). Newer forms of the technology include deep TMS where the

magnetic field is generated from multiple sources allowing for deeper brain penetration and theta burst TMS where rTMS is delivered in a pattern allowing for shorted treatment times. For the purposes of this report TMS refers to rTMS unless otherwise stated.

Treatment resistance for major depression

For major depression treatment resistance is broadly defined as a failure to respond to or tolerate antidepressant medication. Each study defines treatment resistance differently. For example, some studies require a failure to respond to at least two antidepressant medications given at the maximum dosage for at least four weeks to meet the definition.

Treatment resistance for schizophrenia

For schizophrenia, treatment resistance is broadly defined as a failure to respond to at least two different classes of antipsychotic drugs given for a minimum of four weeks.

Preface

The Report on evidence for *Transcranial Magnetic Stimulation for Major Depression and Schizophrenia* (the Report) has been commissioned by the NSW Ministry of Health as a nomination of the NSW new health technology evaluation program. A project management group (PMG), including the NSW Health Chief Psychiatrist, key clinicians and representation from the NSW Agency for Clinical Innovation, provided expert advice to inform and evaluate the Report.

The Report is a useful resource when considering local implementation of Transcranial Magnetic Stimulation (TMS) as a new health technology. However, the PMG also considers that it should be read in the context of the following observations:

1. Heterogeneity of the research base, due to variability in treatment protocols, scope (i.e. PICO - population, intervention, comparator, outcome), rigour and quality of studies, leading to differing results and conclusions. For example, some early studies may have used suboptimal TMS, such as a lower duration of treatment or poor coil placement.
2. Optimal TMS treatment can be difficult to achieve within the confines of research protocols, rather than being tailored to individual needs in a clinical setting.
3. The analysis of cost effectiveness generally does not consider functional outcomes due to cognitive or other adverse effects, and hence health economic outcomes such as the ability to return to work or study. These are important considerations in comparing TMS with drug therapy or ECT.
4. Very few research studies include TMS as a first line treatment, for which it has potential due to patient factors of acceptability, tolerability and quality of life outcomes.

August 2017

Executive summary

Purpose of the review

This Evidence Check review was commissioned by the NSW Ministry of Health to review the evidence of transcranial magnetic stimulation (TMS) for patients with major depression and schizophrenia. The focus is on the intervention's clinical efficacy, safety and cost-effectiveness in these two patient populations and to identify evidence of its use within particular patient subgroups.

The NSW Ministry of Health will use this Evidence Check to assist with decision-making regarding the introduction of this technology into the NSW public health system for the treatment of major depression and/or schizophrenia.

Review questions

This review aimed to address the following questions:

1. For major depression, what is the evidence for the safety, effectiveness and cost-effectiveness of TMS treatment?
2. For major depression is there any evidence that TMS is more effective in particular patient sub-groups than others?
3. For schizophrenia, what is the evidence for the safety, effectiveness and cost-effectiveness of TMS treatment to reduce negative symptoms (including cognition) and auditory hallucinations?

Summary of methods

We conducted comprehensive searches on the 11th of January 2017. We then applied search filters to focus results to systematic reviews, health technology assessments, meta-analyses and randomised controlled trials (RCTs). We used this evidence base to address the three research questions.

We used a two-tiered strategy for study extraction: at the first level, we extracted high-level study characteristics to identify the most recent and relevant studies; then, at the second level those studies we selected from tier one were fully extracted to form the evidence base reported herein.

Key findings

Q1: For major depression, what is the evidence for the safety, effectiveness and cost-effectiveness of TMS treatment?

- There is a considerable evidence base examining TMS for the treatment of major depression over the 10-year period (49 systematic reviews)
- Although this represents a wealth of information, there is a significant degree of variability across this entire pool of literature (for both primary studies and reviews). This is due to the complexity of the treatment protocols as well as the scope (e.g. definition of the population/ intervention/ comparator/ outcome [PICO]), rigour and quality of all studies, and the chronology of each systematic review. The consequence of these factors is that, even though studies examined patients receiving TMS for major depression, their respective results and conclusions were often quite different.
- To account for this variability and to achieve a more consistent conclusion, our two-tiered strategy allowed for a high-level review of the entire evidence base with a more detailed extraction of studies which had been identified as being the most recent and most representative
- Population characteristics were heterogeneous but generally focussed on middle-aged adults suffering

from unipolar major depression

- Patients suffering from treatment resistant depression were a key population, although the definition of treatment resistance was inconsistent
- Patients with bipolar depression were not a focus of this review, but were included and not reported separately by some included studies
- Repetitive TMS is the main intervention, with patients remaining on pharmacological therapy during the course of treatment. Treatment protocols and TMS settings were substantially diverse, which suggests that an optimal TMS protocol is yet to be determined. However, evidence suggests no material difference in outcomes between different treatment protocols and settings
- TMS is safe and generally well-tolerated. Reported adverse events were in general minor and included headache and facial muscle twitching
- Over half of the systematic reviews found that TMS was better than sham for major depression; however, the overall evidence strength was low due to inconsistencies in TMS protocols and large heterogeneities found in meta-analyses
- TMS is more cost-effective when compared to sham but not when compared to Electroconvulsive Therapy (ECT).

Q2: For major depression is there any evidence that TMS is more effective in particular patient sub-groups than others?

- For patients with major depression, there is evidence that age, gender, history of major depression, co-morbid anxiety disorder, co-treatment with anti-psychotics and co-treatment with benzodiazepines do not influence the effectiveness of TMS therapy
- Of particular interest, the severity of depression was also not associated with any effect on patients' response to TMS
- Evidence from studies including a mixed population of major depression and bipolar patients found no difference in treatment response between the two populations
- There is limited evidence that patients with lower levels of treatment resistance, patients with a shorter duration of current depressive episode and patients taking lithium as a co-treatment may respond better to TMS treatment than patients in the broader population
- There is limited evidence that patients with major depression and co-morbid panic disorder or suicidal ideation may not respond as well to TMS therapy as those patients in the broader population.
- It appears that in comparison to ECT, TMS may not be an effective treatment for patients with psychotic depression
- These results are based on a small number of studies with small patient enrolment and therefore further research into these subgroups is required to confirm these findings
- While patient age was not associated with response to treatment, there is little evidence in populations aged over 70 years-old; therefore, these results may not be applicable to elderly patients. Further research is required to identify if there is any benefit of TMS for this older demographic
- No material gaps in reported sub-populations were observed, although some sub-populations were better represented than others. Further research would be beneficial for patients older than 65 years of age, patients with suicidal ideation and those with panic disorder.

Q3: For schizophrenia, what is the evidence for the safety, effectiveness and cost-effectiveness of TMS treatment to reduce negative symptoms (including cognition) and auditory hallucinations?

- The evidence base is very large including information from 27 systematic reviews. For schizophrenia, the Evidence Check identified a more consistent theme in relation to safety and effectiveness compared with that for major depression. However, there was a wide range of TMS protocols and outcome measures leading to divergent results and conclusions.
- To account for this variability and to achieve a more consistent conclusion, our two-tiered strategy allowed for a high-level review of the entire evidence base with a more detailed extraction of studies identified as being the most recent and most representative
- Population characteristics in the trials were in general middle-aged adults but broadly slightly younger than depression patients
- All three symptoms including auditory hallucinations, positive and negative symptoms were very common in patients
- Overall, protocols and settings for TMS were more consistent
- Some minor adverse events were observed including headaches and facial muscle twitching in some patients
- TMS is more effective in treating auditory hallucinations, positive and negative (including cognition) symptoms compared to sham, but not when compared to ECT
- A high level of heterogeneity across trials was reported in systematic reviews
- Cost studies were not identified.

Background

This Evidence Check review was commissioned by the NSW Ministry of Health to review the evidence of transcranial magnetic stimulation (TMS) for patients with major depression and schizophrenia. The rapid review focused on the intervention's clinical efficacy, safety and cost-effectiveness in these patient populations, and to identify evidence of its use within particular patient subgroups for major depression.

The NSW Ministry of Health will use this Evidence Check to assist with decision making regarding the introduction of this technology into the NSW public health system for the treatment of major depression and schizophrenia.

Major depression

In any given year, one in five adult Australians will experience mental illness. Approximately one million Australians live with depression, which affects their wellbeing, personal relationships, career and productivity.[8] The prevalence of depression is slightly higher in women.[9]

Major depression, which is also called major depressive disorder, clinical depression and unipolar depression, is a severe and disabling condition with high levels of morbidity and mortality. The disease is characterised by depressed mood, anhedonia (inability to experience pleasure from usually pleasurable activities) and associated with a number of somatic, vegetative and psychological symptoms. Depression can be described as mild, moderate or severe based on severity.[10]

The American Psychiatric Association's fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), and the World Health Organization's International Statistical Classification of Diseases (ICD-10) criteria are widely used for diagnosis and classification of major depression.[11, 12]

Schizophrenia

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels, and behaves. People with schizophrenia may seem like they have lost touch with reality. While the exact aetiology is unknown, environmental factors such as sedentary lifestyle, drug use, certain infections and genetic factors are believed to have a role in the development of the disease.[13]

Schizophrenia ranks among the top ten causes of disability in developed countries worldwide. In Australia, approximately one per cent of the population have or will develop schizophrenia during their lifetime.[14]

The disease is characterised by presence of positive, negative and cognitive symptoms.[15] Positive symptoms or psychotic symptoms include: delusions, hallucinations, thought disorders (unusual or dysfunctional ways of thinking), and movement disorders (agitated body movements). Negative symptoms include: "Flat affect" (reduced expression of emotions via facial expression or voice tone), reduced feelings of pleasure in everyday life, difficulty beginning and sustaining activities and diminished speaking. Cognitive symptoms arise as a result of deficits in memory, attention and learning ability.

As with depression, schizophrenia is diagnosed based on DSM-V and ICD-10 criteria.

Management

For the management of depression during initial depressive episodes patients receive pharmacotherapy and psychosocial therapy based on severity of symptoms, underlying disorders, prior treatment experience and patient preference. Antidepressants are recommended as the initial treatment option. While the majority of patients respond well to these treatments, approximately 30 per cent of depressed patients will not. Those patients are known to have treatment resistant depression (TRD).[16, 17]

Standard treatment options for schizophrenia include antipsychotic medications, counselling and rehabilitation. However, antipsychotics do not significantly improve the negative symptoms and cognitive function in these patients; therefore, other treatments are also considered. [18]

While pharmacological therapies remain the primary management option for depression and schizophrenia, 20-40 per cent of patients with major depression and schizophrenia respond sub-optimally.[19] Depending on circumstances, other non-pharmacological therapeutic options include electroconvulsive therapy (ECT), transcranial direct-current stimulation (DTS) and Transcranial Magnetic Stimulation (TMS).

ECT is currently the primary management option for TRD and for the negative symptoms of schizophrenia. It is, however, associated with significant side effects and requires the use of general anaesthesia and the management of seizures.[20, 21]

Transcranial magnetic stimulation (TMS)

TMS has been used for over three decades. The procedure uses a coil of wire near the scalp to generate magnetic fields; these in turn induce electrical currents within the brain.[22] These currents depolarize nerve fibres and, when applied repetitively, can decrease or increase cortical excitability — depending on the parameters of stimulation. [23]

TMS can be applied one stimulus at a time (single-pulse TMS), in pairs of stimuli separated by a variable interval (paired-pulse TMS), or in trains, which is also known as repetitive TMS (rTMS) — the latter being the most common stimulation setting in clinical practice.[24] rTMS is believed to have more prolonged effects on the modulation of cortical excitability in managing severe psychiatric diseases. It can be applied as high (5 – 20 Hz) or low (≤1 Hz) frequency.[25, 26]

Methods

The aim of this review was to assess peer-reviewed literature published within the last ten years concerning the safety, clinical efficacy and cost-effectiveness of TMS in the treatment of major depression and schizophrenia. This review examined systematic review and RCT studies and summarises the available evidence, reporting on the extent of the literature and identified gaps.

This review answers the following research questions:

1. For major depression, what is the evidence for the safety, effectiveness and cost-effectiveness of TMS treatment?
2. For major depression, is there any evidence that TMS is more effective in particular patient sub-groups than others?
3. For schizophrenia, what is the evidence for the safety, effectiveness and cost-effectiveness of TMS treatment to reduce negative symptoms (including cognition) and auditory hallucinations?

Criteria for selecting studies

We conducted two unique and separate searches, the details of which are reported in Table 5, Table 6 and Table 7 (Appendix A). The first search identified systematic reviews and meta-analyses and the second identified any RCTs. These searches were undertaken in Embase (Ovid platform), PsycINFO (Ovid platform), PubMed, *The Cochrane Library* and The University of York Centre for Reviews and Dissemination (CRD) databases.

We used Medical Subject Headings (MeSH) terms and keywords to identify relevant literature. We also restricted database searches to English language, human studies published during the last ten years. The search filters were applied using existing strategies from the Canadian Agency for Drugs and Technologies in Health.[27] We rated the quality of included studies (level of evidence) in accordance with NHMRC guidelines.[28]

Evidence extraction and synthesis

We included all relevant studies on either major depression or schizophrenia in this report. For questions 1 and 3, we performed data extraction across two tiers. The first tier extraction was used to describe the entire evidence base at a high level. Information in the first tier was then collated to produce an evidence map which we used to identify the most recent and relevant studies for further investigation in the second tier.

In the second tier, further detail was extracted in accordance with the PICO criteria (Table 1), including patient-related information on age, gender, diagnostic criteria, and status and treatment history. Parameters of TMS protocol were also extracted. This included stimulation focus, laterality, frequency, intensity and durations. Lastly, where reported meta-analyses, point estimates and associated information (confidence intervals, heterogeneities etc.) were also extracted. All the information was tabulated.

For question 2, data was extracted from all relevant RCTs.

Table 1 PICO table

Population	Adults or youth suffering from depression or schizophrenia
Intervention	All forms of TMS with or without adjunct or complimentary interventions
Comparator(s)	Any alternative therapy including but not limited to electroconvulsive therapy, drug management or sham procedure, or alternative TMS protocol
Outcomes	Effectiveness and safety outcomes relevant to depression or schizophrenia
Study type	Systematic reviews, meta-analyses, health technology assessments and RCTs
Publication date	2006 onwards
Language	English language only

Note: PICO = population, intervention, comparator and outcome; TMS = Transcranial magnetic stimulation

Findings

Summary of available evidence

The level of evidence of included studies for this review was high, represented by large numbers of level I and level II studies which were able to inform all of the research questions. Due to the large numbers of available studies, the limited time in which to conduct the review and the need to adhere to standard rapid review methodology, the highest level of evidence available was used to answer each question.

One hundred and two studies provided the evidence base for the review. There were 71 systematic reviews for major depression (n=49) and schizophrenia (n=22) (Figure 1). This synthesised evidence base was used to inform questions 1 and 3.

To account for variability across this entire evidence base in terms of study scope, chronology, rigour and quality, we applied a two-tiered strategy that allowed a high-level review of the entire evidence base with a more detailed extraction of studies which we had identified as being the most recent and most representative.

To acquire a complete understanding of all sub-populations reported as part of trials for major depression, RCT evidence was used for question 2 (Figure 2).

PRISMA charts

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowcharts are shown in Figure 1 and Figure 2 on the following pages.

These two charts illustrate the number of records identified, at what stage (and why) studies were excluded and provide the total number of included studies.

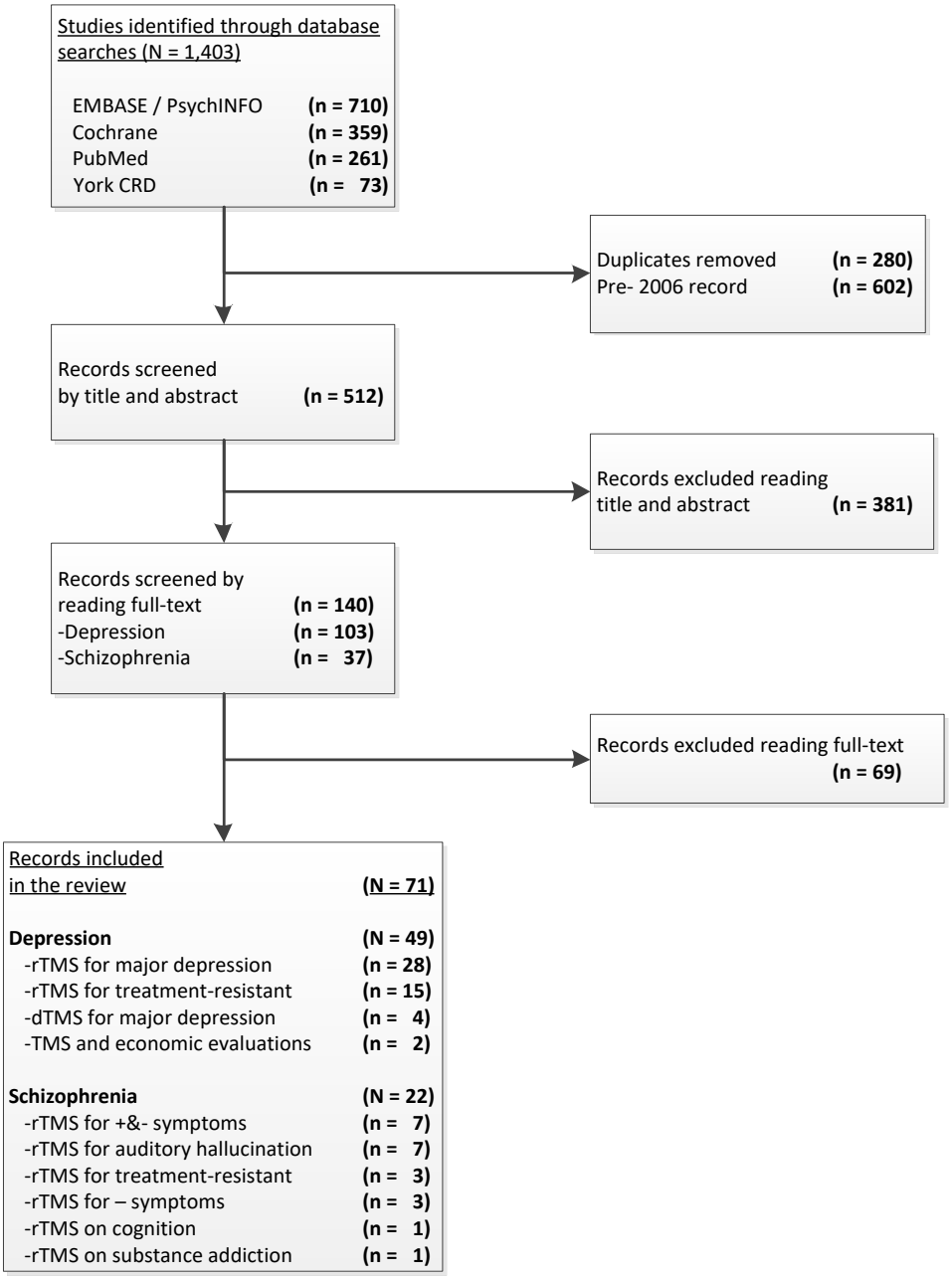

Figure 1: PRISMA flow diagram for systematic reviews

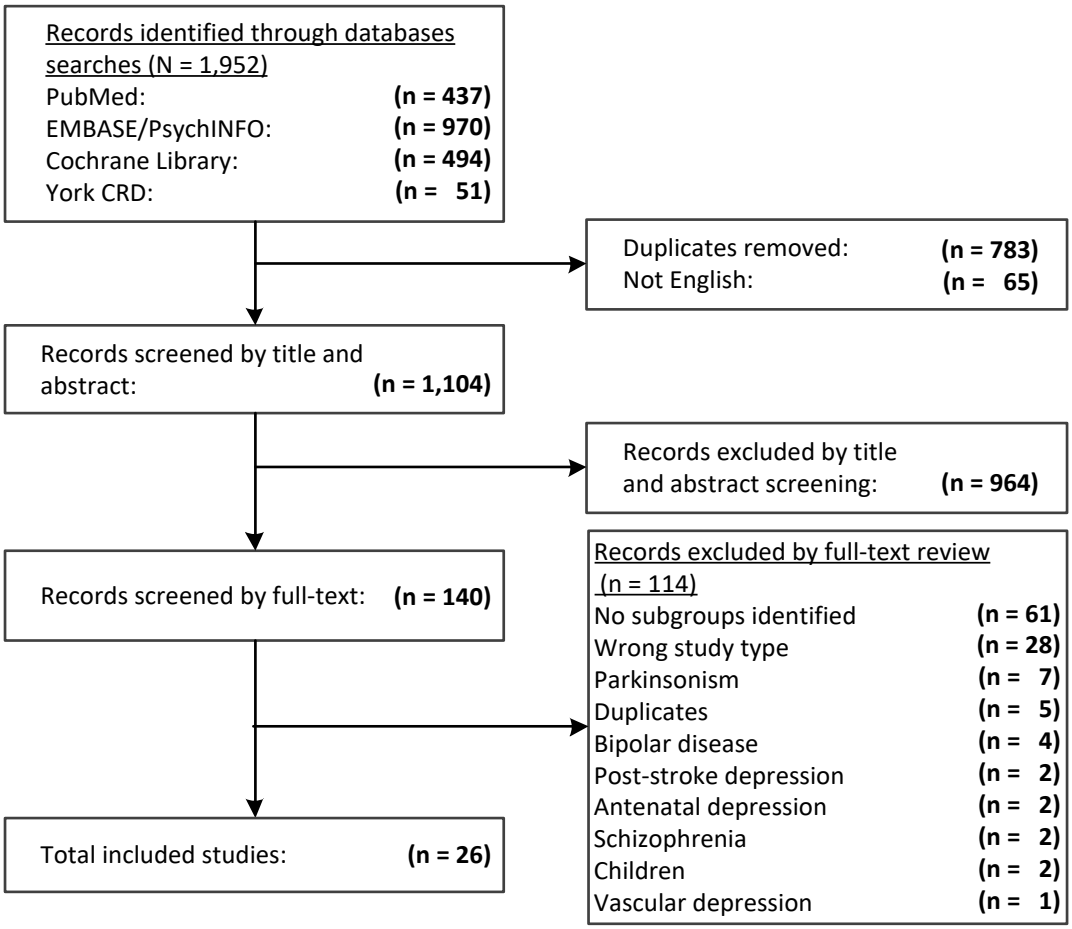

Figure 2: PRISMA flow diagram for RCTs

Question 1: For major depression, what is the evidence for the safety, effectiveness and cost-effectiveness of TMS treatment?

For review question 1, we extracted all systematic reviews reporting on major depression to characterise critical elements of study design and reporting (first tier extraction, Appendix B: Table 12). This evidence base is summarised in the Evidence Map shown in Figure 3 on page 34.

For major depression, 40 reviews were deemed eligible for first tier extraction, including six studies investigating both major depression and schizophrenia.[29-34] Among these studies, 33 reviews included RCTs as their primary studies and the seven reviews were umbrella reviews (including review of existing meta-analyses),[6, 24, 30] narrative summaries of the literature[33, 35] and clinical guidelines with a literature review component.[35, 36] The majority of studies were published post 2010 (n = 35). The size of the reviews in terms of both the number of studies and the number of patients varied. Twelve reviews included less than 10 studies while the largest systematic review (a network meta-analysis) included up to 81 RCTs.[7]

The majority of the reviews focused on repetitive TMS (rTMS); however, three focused on deep TMS (dTMS).[7, 31, 37-39] The parameters within TMS treatment protocols varied substantially across all of the included reviews. This information was targeted at greater detail in the second tier extraction. For most RCTs, sham TMS was used as a control. Open-label studies were also included in some reviews.[31, 35, 40, 41] In regards to the outcome of the reviews, 23 studies claimed that TMS is superior to its comparator in effectiveness. Overall, there were no major safety concerns and no adverse events were reported. To focus on the most up-to-date evidence, five of the most recent reviews were selected for more detailed extraction to address question 1 (Appendix B: Table 8).

Population

The five reviews were broad in terms of inclusion criteria for population characteristics; eligible patients were those with major depression aged over 18 years old. The average age of the populations across studies was approximately 40 years old. Both genders were equally represented.

Most patients were characterised as suffering from TRD. However, the definition of TRD was not consistent. The most frequently used definition for TRD was a failure to respond to at least two rounds of antipsychotic medications;[42, 43] noting that one study defined it as failure to respond up to six rounds.[44] The presence of concurrent mental health issues (OCD and ADHD) was also examined by three reviews[45-47] but excluded by most of the systematic reviews. Two reviews also reported a small proportion of patients with bipolar depression.[7, 42]

TMS treatment protocol

The most commonly reported treatment protocol is high-frequency stimulation on the left dorsal lateral prefrontal cortex (HF-l-DLPFC) combined with low frequency on the right dorsal lateral prefrontal cortex (LF-r-DLPFC). [45, 48, 49] However, the selected five systematic reviews investigated a wide range of settings. Variation in locations, lateralities, frequencies, durations, intensities and session times were identified. The network meta-analyses by Brunoni et al.[7] investigated eight types of TMS including deep and synchronised TMS which were not widely used in other literature. Both high and low frequencies have significant treatment effect and no evidence favoured one level of frequency over another level. The primary focus of the stimulation is on the dorsal lateral prefrontal cortex (DLPFC), and both left and right stimulation can be effective depending on the combinations of other treatment settings. Treatment durations and the number of sessions varied extensively from a few sessions per week[47] up to 20 sessions over more than 4 weeks.[44] The five included studies reported lowest threshold of 80% intensity but this setting also varied up to 120%. Other TMS parameters were also investigated in some reviews such as pulse per sessions. The range of pulses reported varied from 800 to 3000.[43, 47] It should be noted that, irrespective of the treatment protocol, all patients continued with pharmacotherapy.

Safety

No reviews reported any significant safety concerns. The majority reported adverse events were mild and included headache and facial muscle twitching.[50] Therefore, it seems that TMS is a safe procedure for patients with major depression.

Effectiveness

All systematic reviews reported effectiveness outcomes (Appendix B: Table 8). TMS was found to be more effective than sham and different TMS protocols were also compared with each other.[7, 42-44, 47]

TMS compared to sham for major depression

The Hamilton Depression Rating Scale (HDRS) was the most frequently used measurement scale[42, 44, 47] while other scales such as Montgomery–Åsberg Depression Rating Scale (MADRS), Becks Depression Inventory (BDI) and Quick Inventory of Depressive Symptomatology (QIDS) were also used. Gaynes et al.[42] reported significant improvement in HDRS compared to sham, where patients improved by a score of 4.53 in TMS arm (95% confidence interval; -6.11 to -2.96). Among the five studies, two meta-analyses combined different scales into a standardised point estimate and reported the standardised mean difference (SMD). While the SMD was not related to any specific clinical meaning, both studies reported that TMS is significantly better than sham control.[43, 47] This should, however, be interpreted with caution due to the high level of heterogeneity reported (I^2 of up to 88%).[47] Binary outcomes including response and remission rates were also meta-analysed. When TMS was compared to sham, patients were 3.1 times more likely to positively respond to TMS treatment (RR = 3.11, 95% CI = (2.5, 10.3), (I^2 not reported).[42, 44] However, when comparing bilateral TMS with unilateral or sham, there was no significant difference between them in terms of response rate (RR = 1.5, 95% CI = (0.91, 2.47), I^2 = 57%).[44] The remission showed similar patterns. More information is detailed in the second tier extraction (Appendix B: Table 8).

TMS compared to other treatments for major depression

All the five included systematic reviews compared TMS to sham or continued pharmacotherapy (standard care). However, other treatment regimens were also found during the first tier extraction for major depression and one of the widely used treatments is electroconvulsive therapy (ECT). One recent systematic review was selected to represent this comparison.[51]

The evidence for ECT in the treatment of major depression has been well established[51-53] and this therapy has been proven to be effective for treating major depression compared to placebo or sham (anaesthesia).[51, 53, 54] However, possible side effects, including cognitive impairment and tolerability issues, have motivated patients to seek alternatives such as TMS. Chen et al. compared ECT to TMS in a systematic review and network meta-analysis. The review included 25 RCTs with 1288 patients where six RCTs compared ECT to TMS. Similarly, therapy protocols of TMS were considerably varied across the six RCTs included. The review focused on the comparison of ECT to left, right and bilateral TMS. In terms of effectiveness, the network meta-analysis found that ECT had the highest response rate (65%) in comparison to other treatment options; bilateral rTMS = 25%, right rTMS = 8% and left rTMS = 2%. In terms of safety, right rTMS was the most tolerable treatment compared to others while ECT ranked the lowest. The review concluded that ECT was the most efficacious but least tolerated treatment for patients, whereas bilateral rTMS had the most favourable balance in terms of safety and effectiveness.[51]

Innovative and newly emerged TMS for treatment of major depression

Over the past decade, TMS technology has experienced considerable innovation. A novel alternative to repetitive TMS is deep TMS (dTMS), which has a different delivery system to traditional rTMS; reportedly, enabling it to reach deeper and wider regions of the brain. A recent systematic review investigated the effectiveness of dTMS on short-term antidepressant properties for major depression.[31] The study found that dTMS could alleviate short-term clinical symptoms and improve cognitive functions for patients with major

depression. However, the evidence was based on a low level of evidence and large robust RCTs are yet to be performed.

Newer TMS innovation included "synchronised TMS" and "theta (θ) burst TMS". These emerging therapy options are relatively new and the evidence base currently limited.[7, 37]

Cost-effectiveness of TMS for major depression

Three health economic studies were identified, Vallejo-Torres et al. performed a cost-utility analysis comparing TMS to ECT in the National Health Service, United Kingdom (UK).[55] All patients within the model were clinically diagnosed as having severe major depression with treatment resistance. The study showed that ECT is more cost-effective than TMS, with cost per quality-adjusted life year (QALY) gained approximately equal to £16,858. This result was below the Incremental Cost-Effectiveness Ratio (ICER) threshold at the time in UK (£30,000) and therefore likely to be funded publicly. Alternatively, combining ECT and TMS (using one where the other failed) attained the highest QALY gain but also incurred the highest cost. This cost per QALY was well above the ICER threshold in both UK and Spain, hence unlikely to be publically funded.

The study by Simpson et al. in the United States (US) found that TMS is cost-effective compared to sham with ICER equal to $34,999 (US dollar) per QALY gain.[56] The study also stated that the patients evaluated were treatment resistant and suggested that more cost savings may be expected if patients could receive TMS at an early stage of treatment resistance.

A 2014 Medical Services Advisory Committee (MSAC) report evaluated the cost-effectiveness of TMS compared to standard treatment (continued antidepressant drugs) and ECT. The result showed that in the context of private health in Australia, TMS is dominant compared to standard treatment but not cost-effective compared to ECT.[46]

Therefore, TMS seems to be a cost-effective treatment for major depression when it is used in combination with continued pharmacotherapies but not cost-effective when compared to, or in combination with, ECT.

Applicability to NSW Health

Table 2: NHMRC evidence base matrix for research question 1

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Based on the available evidence, the NHMRC evidence matrix for question 1 is shown in Table 2.

The level of evidence used in answering the first research question is high as all the included studies are systematic reviews. However, mainly as a consequence of the broad scope of the research question, there are a considerable number of inconsistencies in the evidence base, depending on the clinical use of TMS and varied population characteristics. This is reflected in Table 2 where more than one box has been highlighted for certain domains. The population of patients suffering from major depression is heterogeneous. The definition of included populations varies across reviews and RCTs (for example in terms of treatment resistance), and the selection of patients that receive TMS in NSW should be clearly defined. The protocols and technical application of TMS varies between study centres. Although the evidence suggests that these technical differences do not have significant impact on TMS therapy, a clear prescription of local practice should be defined. Therefore, the clinical impact is variable and it may depend on how TMS is prescribed based on local guidelines to the appropriate patient groups. The outcomes in the evidence base were relatively generalisable as all the systematic reviews were non-specific in their patient selection and TMS treatment protocols. This reflects both the uncertainties around the appropriate sub-groups as well as the lack of clarity about which types of depression are most responsive.

Overall, the evidence base is applicable to the NSW health system, although there is a consistent theme of variability across certain domains such as patient characteristics, TMS treatment protocols and outcomes used to measure safety, effectiveness and cost-effectiveness.

Question 2: For major depression is there any evidence that TMS is more effective in particular patient sub-groups than others?

The evidence base included 26 RCTs that reported the comparative effectiveness of TMS in at least one subgroup of patients; 15 studies included only patients with unipolar major depression and 11 studies included patients with unipolar major depression and bipolar disorder (Figure 4).[57-67]
Data on the most relevant subgroups is reported below and the extraction table for subgroups is shown in Appendix B: Table 9.

Age

Six RCTs, including 716 patients, investigated the impact of patient age on therapy effectiveness.[68-73] Repetitive TMS was compared to sham therapy in all of the studies. All RCTs identified that patient age was not a predictor of effectiveness. (Appendix B: Table 9)

A total of 104 patients aged between 40 and 65 years old were enrolled in two RCTs (n = 30 and n = 74).[74,75] Results reported in each study identified that TMS was more effective for the treatment of major depression than sham therapy. This is consistent with the overall results reported for question 1 that TMS is more effective than sham therapy and further indicates that the age of patients (up to 65 years old) do not influence whether treatment is effective.

This review has identified that patients aged over 65 years old are potentially understudied. No study reported a separate analysis of the effectiveness of TMS in patients aged over 65 years old. Most studies reporting that age was not correlated with treatment effectiveness included patients over 65 years old but capped enrolment at 70 years old. This subgroup would benefit from further research prior to any conclusions being made on the safety and effectiveness of TMS.

Gender

Four RCTs, including 443 patients, investigated whether patients' gender had any influence on the effectiveness of the therapy.[69, 71-73] All four studies compared TMS to sham therapy. Gender was not a predictor of treatment effectiveness in any study. (Appendix B: Table 9)

One RCT only included female patients (n = 19); in this population, TMS was associated with a superior reduction in depressive symptoms compared to sham therapy.[76] This is consistent with the results from the systematic reviews on the effectiveness of TMS compared to sham in the broad population.

Severity of depression prior to treatment

Five RCTS, including 744 patients, reported on whether the patients' baseline major depression severity was associated with the effectiveness of the treatment.[69, 71-73, 77] In each study TMS was compared to sham therapy. No relationship between depression severity and treatment effect was found by any of the studies. (Appendix B: Table 9)

Treatment resistant depression

Four RCTS, including 761 patients, investigated whether severity of treatment resistance to prior pharmacological treatments had an influence on the effectiveness of TMS.[70-72, 78] Treatment resistance was defined as a failure of prior treatments to alleviate major depression or a failure to tolerate other major depression treatments. Three studies compared TMS to sham therapy[70-72] while the fourth compared deep TMS to sham therapy.[78] Levkowvitz et al. (n = 212) compared patients with major depression resistant to one or two prior treatments to patients with major depression resistant to three or four prior treatments.

Patients with higher resistance tended to be less responsive to deep TMS (statistical significance was not reported).[78] Lisanby et al. (n = 301) compared patients who had received a complete course of a single prior treatment to those who had received a complete course of more than one prior treatment.[71] Superior outcomes from TMS were found for patients who had only tried a single treatment (p = 0.021). Alternatively, George et al.[70] (n = 199) and Philip et al.[72] (n = 49) found that treatment resistance was not a predictor of TMS success.

Duration of current episode

Three RCTs, including 550 patients, investigated whether the duration of the current major depression episode affected response to TMS treatment.[69-71] Lisanby et al. (n = 301) compared patients whose current depressive episode was less than two years in duration to those whose current episode was greater than two years in duration.[71] A greater treatment effect was found for patients in the shorter duration group (p = 0.0015). Duprat et al. (n = 50) and George et al. (n = 149) both found that duration of current depressive episode had no influence on treatment effectiveness.[69, 70]

History of major depression

Two RCTs investigated whether the number of previous major depression episodes influenced the effectiveness of TMS.[69, 71] Lisanby et al. (2009) compared 301 patients in their first major depression episode to those with recurrent illness.[71] Duprat et al. (2016) (n = 50) compared the mean number of depressive episodes in patients who responded to treatment compared to non-responders.[69] Both studies found that major depression history did not influence treatment effectiveness.

Comorbidities

Three RCTs investigated whether a comorbidity influenced the effectiveness of TMS treatment.[71, 79, 80] Desmyter et al. randomised 12 patients to either repetitive TMS or sham therapy. All included patients had suicidal ideation along with major depression. In this population TMS was no more effective at treating major depression than sham therapy.[79] This is not consistent with results in the broad population and may indicate that TMS is not an effective treatment for patients with major depression and suicidal ideation; however, this is a very small RCT and therefore further research in this group is required before any conclusions can be drawn.

Mantovani et al. randomised 25 patients with major depression and panic disorder to either TMS or sham therapy. TMS was not significantly better than sham therapy at treating depression symptoms (p value not reported); however, there was a significant improvement in symptoms of panic disorder (p=0.005).[80] This is not consistent with results in the broad population and may indicate that TMS is not an effective treatment for patients with major depression and panic disorder, although the results suggest that TMS may offer some other benefits to these patients. Again, these results are based on a small RCT and further research is required to confirm these results.

Lisanby et al. randomised 301 patients with major depression to TMS or sham therapy. The authors conducted a subgroup analysis to assess whether patients who also had anxiety disorder responded differently to TMS than those without anxiety disorder.[71] They found that the presence of anxiety did not influence whether TMS was an effective treatment (p = 0.420).

Combination treatments

Two RCTs investigated whether subpopulations of patients with major depression who were taking additional medication at the same time as receiving TMS responded differently to the treatment than patients not receiving combination treatment.[69, 73]

Urllich et al. randomised 43 patients to repetitive TMS or sham therapy and investigated the effect of co-treatment with mood stabilisers (lithium), anti-psychosis medication and benzodiazepines.[73] Patients

receiving lithium had a significantly better response to TMS than those not taking lithium (p = 0.0018). Co-treatment with anti-psychotics and benzodiazepines did not influence treatment effectiveness. Similarly, Duprat et al. found that co-treatment with benzodiazepines did not influence TMS effectiveness in an RCT of 50 patients with major depression.[69]

Bipolar disorder

While outside the scope of this review, TMS has been studied to assess its effectiveness as a treatment for depression in patients with bipolar disorder. Eleven RCTs, with 868 patients, were identified that included a mix of patients with major depression and bipolar disorder.[57-67] These studies have been included herein as their focus was on the use of TMS to treat depressive symptoms and therefore their findings may be of interest.

Three RCTs that included patients with bipolar disorder analysed the comparative effectiveness of TMS. Fitzgerald et al.[62] compared bilateral TMS with unilateral TMS in 179 patients, Chistyakov et al. [57]compared theta burst TMS to sham therapy in 29 patients and Ray et al.[67] compared TMS to sham therapy in 45 patients. All three studies found that there was an equivalent response to TMS in both major depression and bipolar patients. This indicates that results from the mixed population studies can provide information on subgroups where TMS may have different effectiveness to that observed in the broad population of adult patients with major depression; therefore, the subgroup analysis from these RCTs is briefly described below.

Age

Seven RCTs including 720 patients investigated the influence of patient age on the effectiveness of TMS.[58-63, 66] All studies reported that age was not associated with the effectiveness of the treatment. This is consistent with the results from studies including only patients with unipolar major depression.

Age of major depression onset

Four RCTs, including 318 patients investigated the influence of age of onset on TMS effectiveness.[60-62, 66] Three RCTs reported no impact on the results;[60-62] however, Nongpiur et al.[66] found that age of depression onset did influence the effectiveness of the TMS treatment, with patients whose disease onset at an earlier age experiencing a greater reduction in depression following TMS.

Gender

Four RCTs, including 574 patients, investigated whether the effectiveness of TMS was influenced by patient gender in a population of patients with major depression or bipolar disorder.[59, 61-63] No study reported any association between gender and treatment effectiveness. This is consistent with the results from studies that only included patients with major depression.

Duration of current episode

Three RCTs, including 149 patients reported that the duration of the current depressive episode was not a predictor of the effectiveness of the TMS treatment.[60, 61, 66] This result is consistent with the findings of two out of the three RCTs of patients with major depression that investigated this subgroup.

History of major depression

One RCT with 60 patients reported that the number of prior depressive episodes experienced by a patient did not influence the effectiveness of the TMS treatment.[60] This is consistent with the results from studies that only included patients with major depression.

Comorbidities

Four RCTs including a total of 507 patients assessed the influence that comorbidities had on the effectiveness of TMS treatment.[59-62] Comorbidities assessed included anxiety disorder (3 RCTs),[59, 60, 62] panic disorder (2 RCTs),[61, 62] social phobia (2 RCTs),[60, 61] obsessive compulsive disorder (2 RCTs),[61, 62] post-traumatic

stress disorder (2 RCTs),[61, 62] melancholic subtype (2 RCTs),[61, 62] psychosis (1 RCT)[62] and personality disorder (1 RCT)[59]. All studies reported that these comorbidities did not influence the effectiveness of the TMS therapy. These results may be inconsistent with the results of studies including only patients with major depression; however, as noted previously, these findings are based on single, small, RCTs and therefore may not be more widely applicable.

Previous ECT

One RCT with 179 patients investigated the impact of TMS in patients who had previously received ECT.[62] No differences were found between these patients and those who had no prior ECT.

Combination treatments

Five RCTs with 634 patients investigated the impact of co-treatment with anti-depressant medication;[59-63] three RCTs with 314 patients investigated co-treatment with anti-psychosis medication;[58, 59, 61] two RCTs with 95 patients investigated the impact of benzodiazepines[58, 61] and three RCTs with 447 patients investigated the impact of mood-stabilisers.[59, 61, 62] All studies reported that co-treatment with any of the listed medication classes did not impact the effectiveness of the TMS treatment. This is consistent with the results from studies that only included patients with major depression except for a single RCT which reported TMS is more effective in patients taking lithium as a co-treatment.

Postnatal depression

Myczkowski et al. included 14 women who had given birth one to six months prior. These patients were randomised to receive either TMS or sham therapy.[65] Patients in the TMS group showed a significantly greater improvement in depressive symptoms (HDRS scale, $p = 0.02$) suggesting TMS may be beneficial for treating depression post-partum.

Psychosis

Three RCTs with 453 patients investigated whether psychosis (as a comorbidity in patients with either bipolar disorder or major depression) affected treatment results.[58, 60, 67] Eranti et al. reported that ECT was more effective than TMS; noting this was unrelated to whether patients also had a diagnosis of psychosis.[58] Ray et al. reported no difference in the effectiveness of TMS compared to sham in patients with psychosis compared to those without.[67] Fitzgerald et al. reported that psychosis had no impact on treatment effectiveness when comparing bilateral and unilateral TMS.[62]

Major depression with psychosis

The effectiveness of TMS therapy for psychosis was seldom and poorly reported in the RCTs, with only three specifically reporting on this population. This is likely due to the majority of research being conducted before 2007 (noting this report was date limited to studies published in the last 10 years). Each of the three identified RCTs are reported in the section above.

A total of 51 systematic reviews were examined for information on psychosis; 2 were included as they contained the most comprehensive set of relevant studies;[40, 53] 9 systematic reviews duplicated this data;[6, 32, 43, 46, 52, 81-84] and 40 did not report relevant information regarding major depression with psychosis.

Ren et al. investigated the effectiveness of TMS compared to ECT, including six studies with at least some patients with psychotic depression, compared to results in two trials excluding patients with psychotic depression. Results for both remission and response indicated that ECT was more effective than TMS in studies including patients with psychotic depression (response rate ECT 66.7% vs TMS 33.3%). Both treatments achieved similar effectiveness in patients with non-psychotic depression (response rate ECT 51.4% vs TMS 52.5%). [53]

Kedzior et al. investigated the effectiveness of TMS compared to sham TMS in five RCTs, including at least some patients with psychotic depression, to results from 23 RCTs excluding patients with psychotic depression. TMS was associated with a significant reduction in depression scores in studies that excluded patients with psychotic depression (change -0.58, 95% CI -0.77, -0.40, p = <0.001). TMS did not significantly reduce depression in studies that included patients with psychotic depression (change -0.51, 95% CI = -1.14, 0.13, p = 0.117). However, the authors found that the differences between the two groups did not reach the level of statistical significance (p= 0.745).[40]

Overall, it appears that TMS may not be an effective treatment for patients with psychotic depression, while ECT does appear to be effective in this group. Results from the other systematic reviews investigating this population were consistent with these findings.

Strength of the evidence for question 2

The summary of the overall quality of the evidence base is described in Table 3. Overall, the results for each subgroup are informed by a different evidence base. This is reflected in the table where more than one box has been highlighted for certain domains. For subgroups that were commonly reported (for example age, gender) the evidence base is considered good, while for subgroups that were only reported in a single small RCT the evidence base is considered satisfactory. While the results of the subgroup analysis were mostly consistent, the clinical impact, generalisability and applicability for each subgroup need to be viewed in light of the small evidence base available for some groups; therefore, a good to poor rating was judged most appropriate for these categories.

Applicability of the evidence to NSW Health

Overall, the effectiveness of TMS was not dependent on patient characteristics (the examined subgroups). The applicability of these findings to NSW Health is dependent on the available evidence for each subgroup. For patients with major depression, most of the commonly reported subgroups contained some patients recruited from Australian centres, the results of which were reported in the multicentre study by Lisanby et al.[71] and are likely to be applicable to the Australian context. The majority of the evidence base was comprised of patients recruited from OECD countries in Europe and North America, which are also considered to be broadly applicable to Australia. The TMS protocols varied between studies and may not reflect how the technology would be used in NSW; however, no notable applicability red flags were identified. The patient populations recruited into the RCTs may be more restricted than the population of patients who would be eligible for TMS in NSW; however, this is a typical issue with trial design and no extraordinary exclusion criteria were noted that may unduly affect the applicability of the results.

Table 3: NHMRC evidence base matrix for RCT evidence for Major Depression

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Question 3: For schizophrenia, what is the evidence for the safety, effectiveness and cost-effectiveness of TMS treatment to reduce negative symptoms (including cognition) and auditory hallucinations?

For review question 3, all systematic reviews reporting on schizophrenia were extracted to characterise critical elements of study design and outcome reporting (first tier extraction, Appendix B: Table 12). This evidence base is summarised in the Evidence Map shown in Figure 3 on page 34.

This Evidence Check identified 26 systematic reviews eligible for first tier extraction. The majority (20 out of 26) of the systematic reviews solely included RCTs and the number of RCTs examined per publication ranged from 6 to 54. Twenty one of the 26 systematic reviews were published after 2010. Similar to research question 1, most of the reviews focused on repetitive TMS as their intervention whereas three studies also investigated deep TMS.[31, 39, 85] The TMS setting varied substantially across all reviews, especially regarding laterality and frequency.

Twenty-one studies used sham as the only comparator[31-33, 86, 87]; 12 found that TMS was superior to the control group, and, 9 identified that the evidence was insufficient to support any solid conclusion (Appendix B: Table 11). Three studies compared TMS to sham and other interventions. Two studies compared TMS to treatments other than sham. Slotema et al. also compared TMS to ECT.[34] No major safety concerns were raised by any of the systematic reviews.

Due to similarities in the methodology, included studies and outcomes reported across the identified systematic reviews, we selected five of the most recent reviews for more detailed extraction to address question 3 (Appendix B: Table 11)

Population

Patient characteristics in the five selected representative reviews were relatively consistent. The age of enrolled participants was similar across reviews (~30 years); however, only one review reported the mean age (36 years ± 2.82 years).[88] One review only included patients aged 16 years and older.[89] Therefore, the included reviews enrolled schizophrenia patients that were typically younger to middle-aged adults. None of the five systematic reviews reported gender ratios.

Auditory hallucinations, positive and negative symptoms were assessed and reported in each of the five reviews. Only patients with auditory hallucinations were included by Otani et al..[88] Negative symptoms were also reported by Hasan et al.[90] and Shi et al.[91] with 11 out of 33 RCTs including them in the former case and 12 out of 16 RCTs in the latter. In the Cochrane Review, positive symptoms were reported by 11 of 41 included studies (n = 333 patients).[85] Pharmacotherapy treatment resistant patients were reported by one systematic review where refractory schizophrenia was defined as patients failing in at least two different classes of antipsychotic drugs at a minimum of four weeks without experiencing significant symptom relief.[88] Comorbidities were not considered or discussed in any of the five systematic reviews.

TMS treatment protocols

Repetitive TMS was the main intervention examined in the systematic reviews. More detailed TMS settings and protocols are available in (Appendix B: Table 11). Although the setting of TMS varied, protocols were more consistent when treating schizophrenia compared with depression.

The left-side treatment was more commonly practised than right or bilateral-TMS.[85, 88-90] The reviews reported that the temporoparietal cortex (TPC) was the most common stimulation site in comparison to other sites such as the DLPFC.[85, 88-91] This is due to the reported relationships between hyperactivities in TPC and auditory hallucination in schizophrenia patients. By normalising the brain activities in TPC, symptoms of auditory hallucination can be improved.[85] The use of both high and low frequencies were reported. Low frequencies were applied more to left TPC to normalise hyperactivities in the TPC;[85, 88, 89] and high

frequencies were applied to left DLPFC in an attempt to increase brain activities in treating negative symptoms.[85, 92]

There were, however, variations in intensities, session numbers and duration reported. Intensity was reported as approximately 80% or greater in 4 to 9 sessions, with TMS treatment duration lasting between 1 to 4 weeks. All patients continued treatment with antipsychotic medication if treatment was initiated before TMS. Nevertheless, an evidence-based optimum TMS protocol is yet to be determined.

Safety

No serious adverse events were reported in the five systematic reviews with only minor discomfort reported such as headaches and facial muscle twitching. Two studies reported that patients treated with TMS were more likely to experience facial and jaw contractions as well as headaches.[85, 89] Zhang et al. reported that headaches were 3.72 times more likely and facial muscle twitching was 15.5 times more likely experienced by patients receiving TMS than sham.[89] Shi et al. also showed similar results.[91]

Effectiveness

Various effectiveness scales were used to measure the effect of TMS for schizophrenia. The most commonly used measures were the Auditory Hallucination Rating Scale (AHRS) and the Positive and Negative Syndrome Scale (PANSS).

Three studies reported that TMS for auditory hallucinations was superior to sham. Zhang et al. reported that TMS therapy can significantly reduce AHRS scores by 0.42 in patients experiencing auditory hallucination (95%CI = (-0.54, -0.20), I^2 = 15%).[89] In the remaining two reviews, standardised measures were used to combine AHRS with other scales including Hallucination Change Scale (HCS) and Scale for Auditory Hallucinations (SAH); these studies reported that patients receiving TMS therapy achieved statistically significant improvements but with high level of heterogeneity.[85, 88] Similarly, three studies reported that TMS significantly improved positive and negative symptoms on the PANSS and its subscales (PANSS+/-).[85, 89, 90]

The Cochrane Review investigated the cognition outcomes between TMS and standard treatment (continued antipsychotic drugs), and no statistically significant differences were found.[85] These findings mirror the findings by Hasan et al. where cognitive functions were not significantly improved by TMS in schizophrenia patients.[85, 90] In addition, a recent Australian systematic review conducted by Martin et al. on TMS in patients with neuropsychiatric conditions examined cognitive function improvement in schizophrenia patients.[93] Although their meta-analysis of data from two unique studies showed a significant improvement in working memory following TMS, overall the study agreed with the conclusion by Hasan et al.[90] and the Cochrane Review [85], showing a less substantial gain in cognitive function resulting from TMS treatment.

Shi et al.[91] also found that the efficacy of TMS was more likely to decrease in patients the longer their duration of illness (eight years or more).

Cost studies of TMS therapy for schizophrenia

We conducted a targeted search in an attempt to identify cost studies of TMS therapy for schizophrenia; however, no studies were identified. This paucity of evidence was also confirmed via clinician feedback (Personal Communication, The University of Adelaide).

Applicability to NSW Health

Overall, the evidence base for question 3 is applicable to the NSW health system. The outcomes in the evidence base were relatively generalisable as the included systematic reviews investigated a broad range of TMS treatment protocols and were non-specific on patient selection in terms of symptoms and subgroups. The level of evidence is high as all the included studies are systematic reviews. The patient population included in the evidence base is relatively consistent, and certain elements within TMS treatment protocols were

commonly practiced. There are, however, areas of variability reflected in Table 4 on the following page where more than one box has been highlighted for certain domains:

- There is a substantial level of uncertainty regarding the appropriate patient population for TMS due to the varied evidence supporting the effectiveness of TMS for specific symptoms (such as auditory hallucinations, positive or negative symptoms)
- The most effective protocol for, and the optimal technical setting of, TMS are yet to be determined.

Due to these uncertainties, the clinical impact is therefore variable; and, its clinical applicability may depend on how TMS is prescribed to specific patient groups and the protocol used in each instance.

The NHMRC evidence matrix for question 3 is shown below (Table 4).

Table 4: NHMRC evidence base matrix for systematic review evidence for schizophrenia

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	several level I or II studies with low risk of bias	one or two level II studies with low risk of bias or a SR/multiple level III studies with low risk of bias	level III studies with low risk of bias, or level I or II studies with moderate risk of bias	level IV studies, or level I to III studies with high risk of bias
Consistency	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

Conclusion

This Evidence Check reviewed a wide spectrum of TMS trials and protocols for the treatment of major depression and schizophrenia. We summarised the extracted systematic review and RCT evidence to highlight the safety, effectiveness and the cost-effectiveness of TMS. As a consequence of the spectrum of trials and protocols reported in the evidence, varying conclusions from similar cohorts were identified. Due to the diversity in the PICO criteria, and the 'rapid' nature of the Evidence Check review, a formal synthesis of data was not undertaken. Despite this variation, some common themes were observed in the literature.

Question 1: For major depression, what is the evidence for the safety, effectiveness and cost-effectiveness of TMS treatment?

For major depression, it appears TMS is more effective in improving depression when compared to sham. Only minor adverse events were reported, such as transient headaches and facial muscle twitching. Although ECT remains as the most effective treatment for major depression, TMS does provide a safe alternative to patients that cannot tolerate ECT. For both these therapeutic options, patients continue to receive ongoing pharmacotherapy. In relation to cost, TMS is more cost-effective when compared to sham or continued pharmacotherapy, but not when compared to ECT. The examination of systematic review evidence identified considerable variation in the evidence base in relation to the populations examined and the parameters of the treatment protocols utilised. It is important to note that, if used in NSW, the clinical impact is likely to vary and it may depend on how TMS is prescribed at a local level.

Question 2: For major depression, is there any evidence that TMS is more effective in particular patient sub-groups than others?

RCT safety and efficacy evidence was examined to identify TMS subgroup population outcomes. A number of patient sub-groups were identified, reflecting the broad range of people who suffer from major depression. It was found that patient characteristics such as age, gender, history of the disease, comorbidities, existence of co-treatment and depression severity are unlikely to influence treatment outcomes. TMS treatment protocols differed between the included studies; therefore, evidence exists for a range of parameters. Consequently, in NSW, the implementation of TMS for patients with major depression should include a clear statement on the characteristics of the target population as well as the parameters of the proposed treatment.

Question 3: For schizophrenia, what is the evidence for the safety, effectiveness and cost-effectiveness of TMS treatment to reduce negative symptoms (including cognition) and auditory hallucinations?

For schizophrenia, the treatment effects of TMS are more definitive. TMS is superior to sham with all patients remaining on their standard treatments. In addition, it appears more targeted and commonly practised TMS protocols are used when treating patients with schizophrenia. This rapid review identified that serious adverse events were uncommon, with only minor discomfort reported such as headaches and facial muscle twitching. No studies on the cost of TMS for schizophrenia were identified. Due to the broad range of findings published, there are facets of research that are applicable to NSW Health.

In summary

TMS is a generally safe and effective alternative therapy for patients with major depression and schizophrenia. NSW Health should note the considerable variability in the evidence base for major depression but less variability for schizophrenia. It should ensure that clinicians specify the population in which they seek to use TMS as well as the parameters of the TMS protocols they intend to use prior to its application. Using this information NSW Health could, if required, perform targeted reviews to overcome the variability in this broad

evidence base, and focus on the respective safety and effectiveness for the specified population and intervention to be targeted in the local context.

Evidence maps

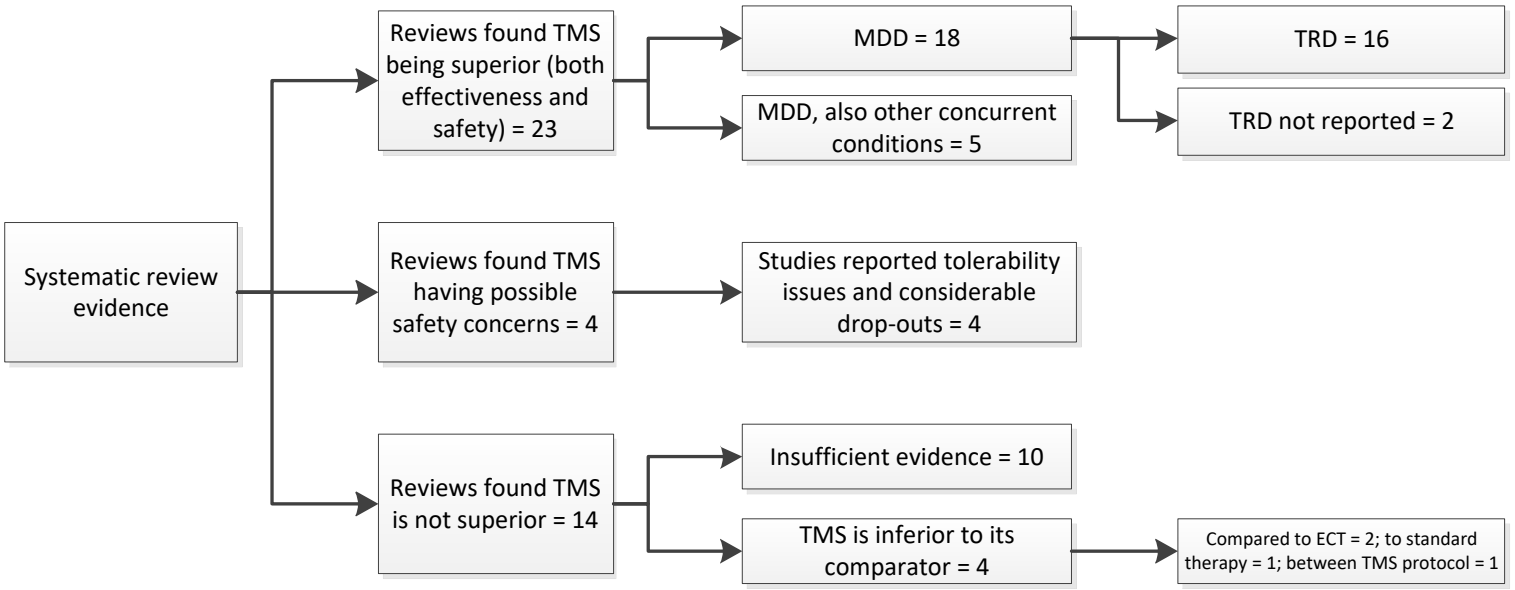

Figure 3 Evidence map for major depressive disorder: systematic reviews

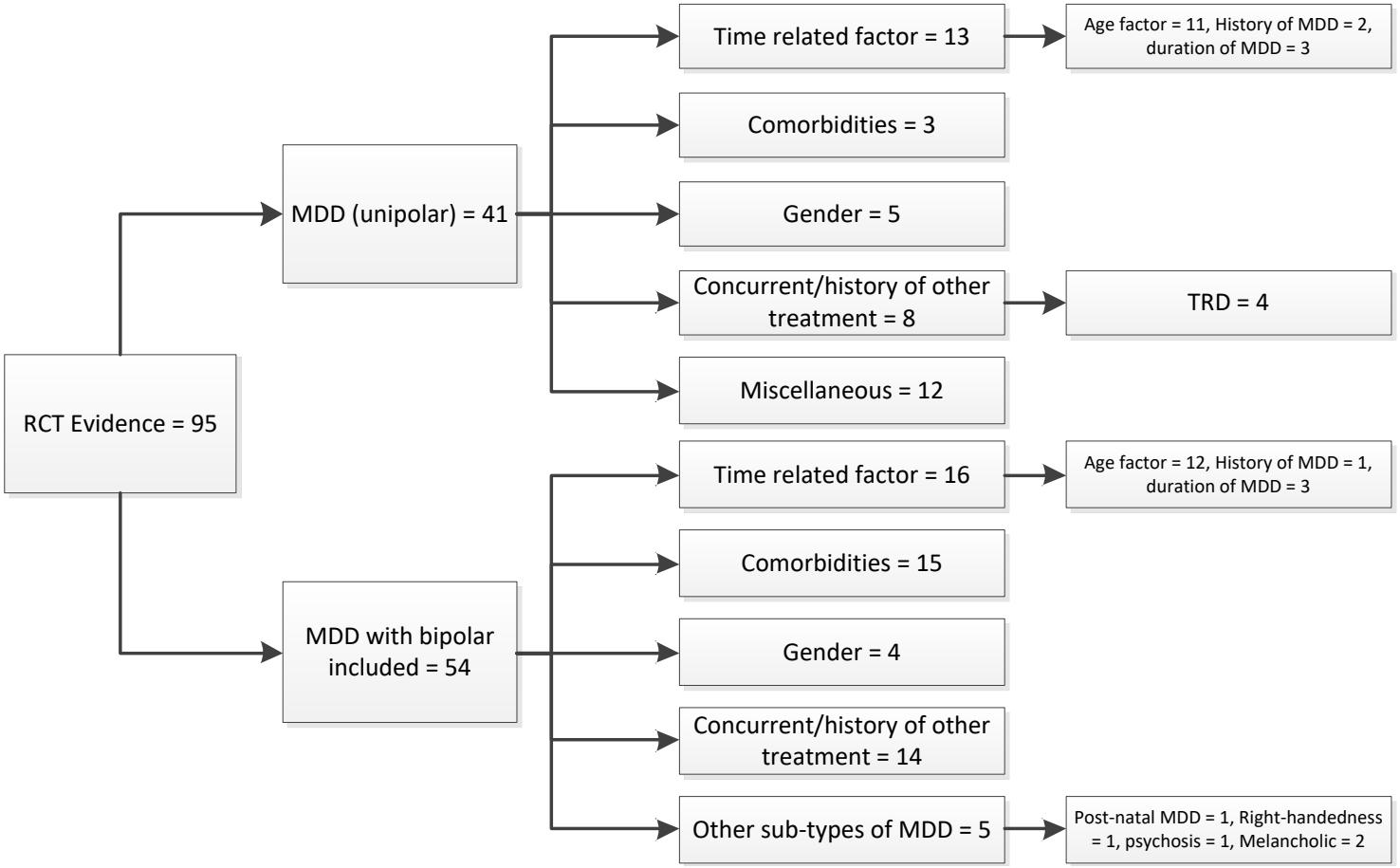

Figure 4: Evidence map for major depressive disorder: randomised controlled trials

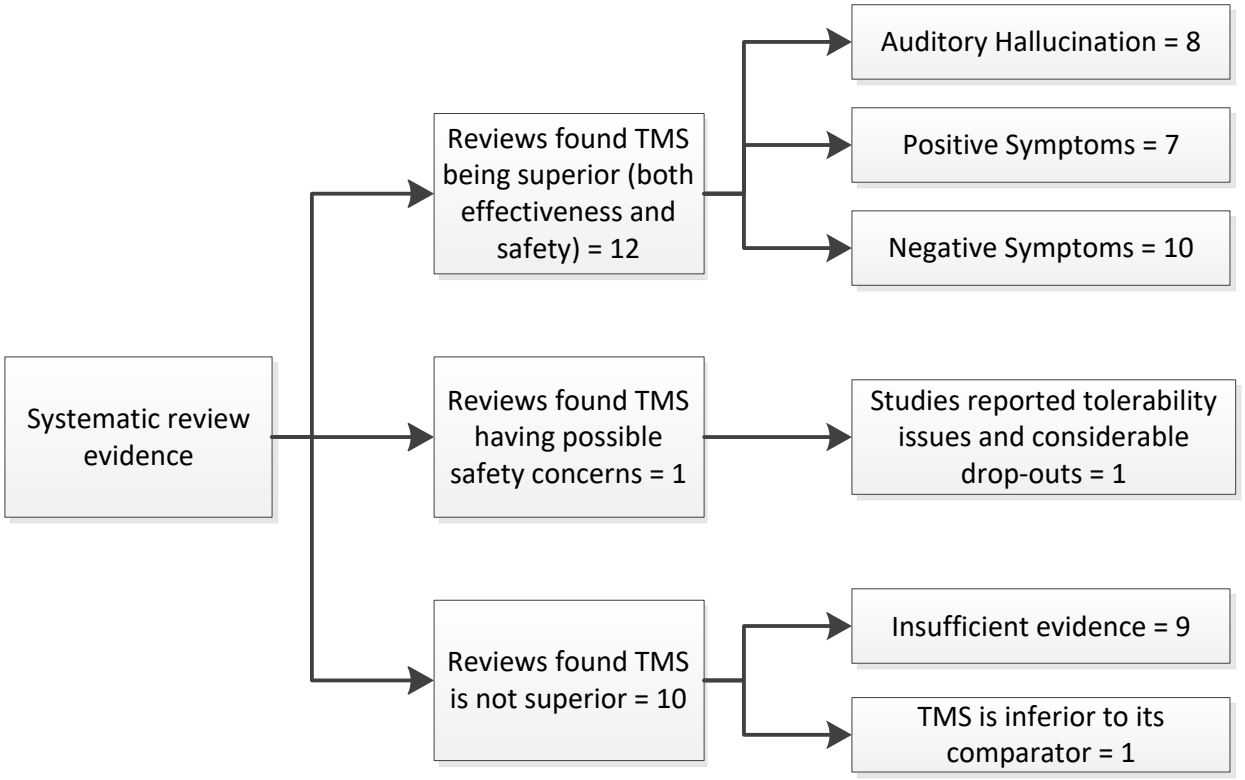

Figure 5: Evidence map for schizophrenia: systematic reviews

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Appendix A

Table 5 Search terms and strategy used for database searches (PubMed)

((Depression[mh] OR Depressive disorder[mh] OR depression OR depress*) OR (Schizophrenia[mh] OR schizophrenia OR schizophren*)) AND (Transcranial magnetic stimulation[mh] OR ((transcranial OR trans-cranial) AND magnetic)) OR tms OR rtms)

Limits: Searched within titles and abstracts, English language, last ten years; humans (adults only)
Study types: systematic reviews, meta-analyses and comparative studies, including randomised controlled trials.

Table 6 Search filters to capture systematic reviews, meta-analyses and health technology assessments (PubMed)

systematic[sb] OR Review Literature as Topic [mh] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR integrative research[tiab] OR integrative review*[tiab] OR integrative overview*[tiab] OR research integration*[tiab] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR technology assessment*[tiab] OR technology overview*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR indirect comparison*[tiab] OR ((indirect treatment[tiab] OR mixed-treatment[tiab]) AND comparison*[tiab]) OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Scopus[tiab] OR Embase[tiab] OR Cinahl[tiab] OR Medline[tiab] OR Pubmed[tiab] OR DARE[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[ta] OR "health technology assessment winchester, england"[ta] OR "Evid Rep Technol Assess (Full Rep)"[ta] OR "Evid Rep Technol Assess (Summ)"[ta] OR "Int J Technol Assess Health Care"[ta] OR "GMS Health Technol Assess"[ta] OR "Health Technol Assess (Rockv)"[ta] OR "Health Technol Assess Rep"[ta] OR jbi database system rev implement rep [ta]) NOT (comment OR letter OR editorial) NOT (animals[mh] NOT humans[mh])

Note: This is an updated CADTH database search filter.[27]

Table 7 Search filters to capture randomised controlled trials (PubMed)

randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random*[tw] OR "Placebos"[Mesh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw]))

Note: This is an updated CADTH database search filter.[27]

Appendix B

Table 8: Extraction table of individual systematic reviews examined in question 1

Author/Year/Title	Study profile	Population characteristics	Intervention rTMS Protocol	Comparator	Safety and Effectiveness	Additional information
Gaynes et al. 2014 Repetitive Transcranial Magnetic Stimulation for Treatment Resistant Depression in Adult and Youth Populations: A Systematic Literature Review and meta-analysis	Systematic review and meta-analysis Included studies = 27 Included patients = not reported	Adults over 18 years Major diagnosis outcomes = HDRS, MADRS, BDI, QIDS TRD = patients failed 2 or more. The review also included a proportion of bipolar disorder patients.	Intervention protocols in this review were mixed regarding location, laterality, and frequency and unclear on the duration of the treatment. The rTMS intensity is 80% or more, and sessions vary from 5 to 20.	All studies were sham controlled. Also other rTMS protocols	**HDRS:** rTMS exclu. bipolar, vs. sham, , model = RE, MD = -4.53, 95%CI = (-6.11, -2.96), Superior. **Response rates:** rTMS exclu. bipolar, vs. sham, model = RE, RR = 3.11, 95%CI = (2.24, 5.10), Superior **Remission:** rTMS exclu. bipolar, vs. sham, , model = RE, RR = 4.31, 95%CI = (2.5, 10.3), Superior.	The review also included major depression /bipolar patients and the data were meta-analysed. The review also included patient with 1 or more/ unclear (probable 2 more) antidepressant meta-analysed them separately: HDRS MD = -4.81, 95%CI = (-6.11, 3.52) I^2 = 78% Superior.

Author/Year/Title	Study profile	Population characteristics	Intervention rTMS Protocol	Comparator	Safety and Effectiveness	Additional information
Kedzior et al. 2015 Durability of the antidepressant effect of the high-frequency repetitive transcranial magnetic stimulation (rTMS) in the absence of maintenance treatment in major depression: a systematic review and meta-analysis of 16 double-blind, randomized, sham-controlled trials.	Systematic review and meta-analysis Included studies = 16 Included patients = 495	Mean age = 40, Range = [32, 61], Female proportion = 60%, Depression onset age mean = 35, Total illness = 17 or more. Major depression diagnosis criteria = DSM-IV, ICD 10 TRD = patients failed 2 or more. 60% studies only included unipolar and up to 40% studies included small proportion of bipolar patients.	The treatment protocol is PFC/DLPFC on the left side, with high frequency (over 5Hz) for 1 to 4 weeks. The intensity is 100% or more. 10-15 acute sessions, PPS = 800-1000 All patients were continued with pharmacotherapy.	All studies were sham controlled	**Standardised Mean difference for all depression scores** rTMS vs. sham, model = RE, N = 16, SMD = -0.48, 95%CI = (-0.70, -0.25), Superior.	Subgroup meta-analyses discovered significant moderators including: Session = 10-15, Intensity <100%, Treatment resistance (2more), LoF = 1-4 weeks. Patients who are unipolar with non-psychotic comorbidities, and younger in age (<40).

Author/Year/Title	Study profile	Population characteristics	Intervention rTMS Protocol	Comparator	Safety and Effectiveness	Additional information
Zhang et al. 2015 Bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis of randomized controlled trials.	Systematic review and meta-analysis Included studies = 10 Included patients = 634	Mean age ranged from 40.45 ± 15.5 to 58 ± 12.5 years Major depression diagnosis criteria (# studies): DSM-IV = 7, ICD = 1, MINI = 2 TRD: patients failed at least 1 drug for 4 or more weeks, to failed 4 drugs for 6 or more weeks.	The rTMS location is on PFC/DLPFC. Laterality and frequency is diversely reported in the included RCTs, Treatment duration lasted from 1 to 4 weeks with 100% more intensity. Bilateral rTMS was a combination of right LF (1Hz)-rTMS with left HF(10Hz)-rTMS or right HF(10Hz)-rTMS with left HF (10Hz)-rTMS. Some studies included 20Hz with longer durations.	7 studies compared to sham 6 studies compared between rTMS protocols.	**Response:** bilateral rTMS vs. others, model = RE, RR = 1.50, 95%CI = (0.91, 2.47); I^2 = 57%, Non-superior **Remission:** bilateral rTMS vs. others, model = RE, RR = 1.47, 95%CI = (0.56, 3.82), I^2 = 72%, Non-superior **Response:** bilateral rTMS vs. sham, model = RE, RR = 3.29, 95%CI = (1.69, 6.38), I^2 = 0%, Superior **Remission:** bilateral rTMS vs. sham, model = RE, RR = 0.50, 95%CI = (0.19, 1.31), I2 = 0%, Non-superior.	Comparisons between bilateral vs. unilateral rTMS were also available but the comparison was not significant.

Author/Year/Title	Study profile	Population characteristics	Intervention rTMS Protocol	Comparator	Safety and Effectiveness	Additional information
Brunoni et al. 2016 Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes A Systematic Review With Network Meta-analysis.	Systematic review and meta-analysis Included studies = 81 Included patients = 4,233.	Mean age = 46 years, female proportion = 59.1% (2,501/4,233) Major depression diagnosis criteria were Not reported. TRD = 74.1% of the included patients were treatment resistant (unclear how many prior failures). Bipolar depression patients and patients with comorbidities (anxiety or personality disorders) were also included.	This review is a network meta-analyses, interventions investigated in this review included: LF-rTMS over the right DLPFC, HF-rTMS over left DLPFC, bilateral rTMS (LF over the right and HF over the left DLPFC), TBS (=θ-burst stimulation, including intermittent TBS over the left DLPFC, continuous over the right DLPFC or bilateral), pTMS over the right DLPFC, aTMS over the left DLPFC, sTMS = synchronized TMS dTMS over left DLPFC.	The review compared the intervention to sham and other rTMS protocols.	Only significant results were extracted here, all compared to sham, response rate as the outcome: Bilateral, OR = 3.39, 95%CI = (1.91, 6.02) HF-rTMS, OR = 3.28, 95%CI = (2.33, 4.61) TBS, OR = 2.57, 95%CI = (1.17, 5.62).	Safety = acceptability rate, over pTMS, Effectiveness = response rate, over sham, All comparisons were direct.

Author/Year/Title	Study profile	Population characteristics	Intervention rTMS Protocol	Comparator	Safety and Effectiveness	Additional information
Teng et al. 2016 High-frequency repetitive transcranial magnetic stimulation (rTMS) over the left DLPFC for major depression: Session-dependent efficacy: A meta-analysis.	Systematic review and meta-analysis Included studies = 30 Included patients = 1,136	Patient inclusion criteria: 18 to 75 years Major depression diagnosis criteria (# studies) =DSM-IV = 26; ICD10 = 4 TRD = not reported Patients with comorbidities of psychotic symptoms were excluded.	All rTMS was applied on DLPFC with over 90% intensity. Laterality and frequency varied from 5Hz to 20 Hz. Session number vary from 5 to 20; PPS varies from 250 to 3,000; rTMS is mostly combined with antipsychotic, but monotherapy exists in 6 studies.	All sham controlled.	**Standardised Mean difference for all depression scores** Model = RE; SMD = -0.73, 95%CI = (-1.00, -0.47), I^2 = 88%, Superior.	Subgroups were meta-analysed by sessions (5, 10, 15, 20) and pulses (1000, 1200-1500, 1600-1800). The optimum dose is 1200 to 1500 pulses regardless the session number.

Abbreviations: aTMS = accelerated TMS, DLPFC = dorsal lateral prefrontal cortex, dTMS = deep TMS , HF-rTMS = high frequency rTMS, LF-rTMS = low frequency rTMS, MDD = major depressive disorder, NR = not reported, pTMS= priming TMS, rTMS = repetitive TMS, sTMS = synchronised TMS, TMS = transcranial magnetic stimulation

Table 9 Effect of TMS in identified subgroups of patients with major depression

Subgroup Author (year) Country	Number of patients	Intervention		Comparator		Is TMS more effective in the subgroup?
		rTMS	Other*	Sham	Other*	
Age						
Blumberger et al. (2012) Canada	74	✓	-	✓	-	No (p = 0.58)
Concerto et al. (2015) Italy	30	✓	-	✓	-	No. Results consistent with studies including patients of all ages**
Duprat et al. (2016) Belgium	50	✓	-	✓	-	No (p = NR)
George et al. (2010) USA	199	✓	-	✓	-	No (p = 0.81)
Lisanby et al. (2009) Multicentre (USA, Australia, Canada)	301	✓	-	✓	-	No (p = 0.59)
Philip et al. (2016) USA	49	✓	-	✓	-	No (p = NR)
Ullrich et al. (2012) Germany	43	✓	-	✓	-	No (p = NR)
Zheng et al. (2015) China	32	✓	-	✓	-	No. Results consistent with studies including patients of all ages†
Gender						
Duprat et al. (2016) Belgium	50	✓	-	✓	-	No (p = 0.37)
Lisanby et al. (2009) Multicentre (USA, Australia, Canada)	301	✓	-	✓	-	No (p = 0.94)
Kristic et al. (2014) Serbia	19	✓	-	✓	-	No. Results consistent with studies including male and female patients§
Philip et al. (2016) USA	49	✓	-	✓	-	No (p = NR)

Subgroup Author (year) Country	Number of patients	Intervention		Comparator		Is TMS more effective in the subgroup?
		rTMS	Other*	Sham	Other*	
Ullrich et al. (2012) Germany	43	✓	-	✓	-	No (p = NR)
Severity of depression						
Duprat et al. (2016) Belgium	50	✓	-	✓	-	No (p = 0.43)
Lisanby et al. (2009) Multicentre (USA, Australia, Canada)	301	✓	-	✓	-	No (p = 0.77)
O'Reardon et al. (2007) Canada	301	✓	-	✓	-	No (p = NR)
Philip et al. (2016) USA	49	✓	-	✓	-	No (p = NR)
Ullrich et al. (2012) Germany	43	✓	-	✓	-	No (p = NR)
Treatment resistance						
George et al. (2010) USA	199	✓	-	✓	-	No (p = 0.15)
Levkovitz et al. (2015) Multicentre (USA, Israel, Germany, Canada)	212	-	Deep TMS	✓	-	Yes. Superior effectiveness for patients with less resistance (p = NR)
Lisanby et al. (2009) Multicentre (USA, Australia, Canada)	301	✓	-	✓	-	Yes. Superior effectiveness for patients who trial 1 prior treatment compared to >1 (p = 0.021)
Philip et al. (2016) USA	49	✓	-	✓	-	No (p = NR)
Duration of current episode						
Duprat et al. (2016) Belgium	50	✓	-	✓	-	No (p = 0.16)

Subgroup Author (year) Country	Number of patients	Intervention		Comparator		Is TMS more effective in the subgroup?
		rTMS	Other*	Sham	Other*	
George et al. (2010) USA	199	✓	-	✓	-	No (p = 0.17)
Lisanby et al. (2009) Multicentre (USA, Australia, Canada)	301	✓	-	✓	-	Yes. Superior effectiveness for current episode <2 years (p = 0.0015)
History of major depression						
Duprat et al. (2016) Belgium	50	✓	-	✓	-	No (p = 0.81)
Lisanby et al. (2009) Multicentre (USA, Australia, Canada)	301	✓	-	✓	-	No (p = 0.86)
Co-morbid anxiety						
Lisanby et al. (2009) Multicentre (USA, Australia, Canada)	301	✓	-	✓	-	No (p = 0.42)
Co-morbid panic disorder						
Mantovani et al. (2013) USA	25	✓	-	✓	-	Yes. TMS not superior to sham in this population for MDD. TMS did improve panic disorder symptoms.
Co-morbid suicide ideation						
Desmyter et al. (2014) Belgium	12	✓	-	✓	-	Yes. TMS not superior to sham in this population.
Melancholic subtype MDD						
Duprat et al. (2016) Belgium	50	✓	-	✓	-	No (p = 0.48)
Schrijvers et al. (2012) Belgium	21	✓	-	✓	-	No (p = NR)
Co-treatment anti-psychotics						
Urlich et al. (2012) Germany	43	✓	-	✓	-	No (p = NR)

Subgroup Author (year) Country	Number of patients	Intervention		Comparator		Is TMS more effective in the subgroup?
		rTMS	Other*	Sham	Other*	
Co-treatment benzodiazepines						
Duprat et al. (2016) Belgium	50	✓	-	✓	-	No (p = 0.94)
Urlich et al. (2012) Germany	43	✓	-	✓	-	No (p = NR)
Co-treatment mood stabilisers						
Urlich et al. (2012) Germany	43	✓	-	✓	-	Yes. Co-treatment with lithium was associated with superior effectiveness (p = 0.0018)
Use of correct protocol for TMS						
Leuchter et al. (2015) USA	120	-	Low-field synchronised TMS	✓	-	Yes. Superior results for correct protocol and total treatment compliance
Employment status						
Lisanby et al. (2009) Multicentre (USA, Australia, Canada)	301	✓	-	✓	-	No (p = 0.10)
Hospitalised patients						
Duprat et al. (2016) Germany	50	✓	-	✓	-	No (p = 0.51)

Table notes: * = any intervention other than rTMS, any comparator other than sham therapy, ** = Study only included a subpopulation of patients aged 40-65 years, † = study only included a subpopulation of patients aged 18-40 years, § = study only included a subpopulation of female patients.

Abbreviations: MDD = major depressive disorder, NR = not reported, rTMS = repetitive TMS, TMS = transcranial magnetic stimulation

Table 10: Effect of TMS in identified subgroups of patients with MDD or bipolar disorder

Subgroup Author (year)	Number of patients	Intervention		Comparator		Is TMS more effective in the subgroup?
		rTMS	Other*	Sham	Other*	
Co-morbid bipolar disorder						
Chistyakov et al. (2015) Israel	29	-	Theta-bust TMS	✓	-	No (p = NR)
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Ray et al. (2011) India	45	✓		✓		No (p = NR)
Age						
Eranti et al. (2007) UK	46	✓	-	-	ECT	No (p = 0.10)
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (p = NR)
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Fitzgerald et al. (2011) Australia	219	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Fitzgerald et al. (2008) Australia	60	✓	-	✓	-	No (p = NR)
Herwig et al. (2007) Multicentre (Germany, Austria)	127	✓	-	✓	-	No (p = NR)
Nongpiur et al. (2011) India	40	✓		✓	-	No (p = NR)
Age of MDD onset						
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (p = NR)
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Fitzgerald et al. (2008) Australia	60	✓	-	✓	-	No (p = NR)

Subgroup Author (year)	Number of patients	Intervention		Comparator		Is TMS more effective in the subgroup?
		rTMS	Other*	Sham	Other*	
Nongpiur et al. (2011) India	40	✓		✓	-	Yes. Earlier onset associated with superior effectiveness (p = 0.004)
Gender						
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (p = NR)
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Fitzgerald et al. (2011) Australia	219	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Herwig et al. (2007) Multicentre (Germany, Austria)	127	✓	-	✓	-	No (p = NR)
Duration of current episode						
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (p = NR)
Fitzgerald et al. (2008) Australia	60	✓	-	✓	-	No (p = NR)
Nongpiur et al. (2011) India	40	✓		✓	-	No (p = NR)
History of MDD						
Fitzgerald et al. (2008) Australia	60	✓	-	✓	-	No (p = NR)
Co-morbid anxiety						
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Fitzgerald et al. (2011) Australia	219	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Fitzgerald et al. (2008) Australia	60	✓	-	✓	-	No (p = NR)
Co-morbid panic disorder						

Subgroup Author (year)	Number of patients	Intervention		Comparator		Is TMS more effective in the subgroup?
		rTMS	Other*	Sham	Other*	
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (p = NR)
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Co-morbid social phobia						
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (p = NR)
Fitzgerald et al. (2008) Australia	60	✓	-	✓	-	No (p = NR)
Co-morbid OCD						
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (p = NR)
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Co-morbid PTSD						
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (p = NR)
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Melancholic subtype MDD						
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (p = NR)
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Co-morbid psychosis						
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Co-morbid personality disorder						

Subgroup Author (year)	Number of patients	Intervention		Comparator		Is TMS more effective in the subgroup?
		rTMS	Other*	Sham	Other*	
Fitzgerald et al. (2011) Australia	219	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Previous ECT						
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Co-treatment with anti-depressants						
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (p = NR)
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Fitzgerald et al. (2011) Australia	219	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Fitzgerald et al. (2008) Australia	60	✓	-	✓	-	No (p = NR)
Herwig et al. (2007) Multicentre (Germany and Austria)	127	✓	-	✓	-	No (p = NR)
Co-treatment with anti-psychotics						
Eranti et al. (2007) UK	46	✓	-	-	ECT	No (p = 0.06)
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (p = NR)
Fitzgerald et al. (2011) Australia	219	-	Bilateral rTMS	-	Unilateral rTMS	No (p = NR)
Co-treatment with benzodiazepines						
Eranti et al. (2007) UK	46	✓	-	-	ECT	No (p = 0.35)

Subgroup Author (year)	Number of patients	Intervention		Comparator		Is TMS more effective in the subgroup?
		rTMS	Other*	Sham	Other*	
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (*p* = NR)
Co-treatment with mood stabilisers						
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (*p* = NR)
Fitzgerald et al. (2013) Australia	179	-	Bilateral rTMS	-	Unilateral rTMS	No (*p* = NR)
Fitzgerald et al. (2011) Australia	219	-	Bilateral rTMS	-	Unilateral rTMS	No (*p* = NR)
Postnatal population						
Myczkowski et al. (2012) Brazil	14	✓	-	✓	-	No. TMS was more effective than sham in this population, consistent with results in the broader population.
Right-handed population						
Fitzgerald et al. (2016) Australia	49	✓	-	✓	-	No (*p* = NR)

Table notes: * = any intervention other than rTMS, any comparator other than sham therapy, ** = Study only included a subpopulation of patients aged 40-65 years, † = study only included a subpopulation of patients aged 18-40 years, § = study only included a subpopulation of female patients.
Abbreviations: ECT = electroconvulsive therapy, MDD = major depressive disorder, NR = not reported, OCD = obsessive compulsive disorder, PTSD = post-traumatic stress disorder, rTMS = repetitive TMS, TMS = transcranial magnetic stimulation.

Table 11: Extraction table of individual systematic reviews examined in question 3

Author/Year/Title	Study profile	Population characteristics	Intervention rTMS Protocol	Comparator	Safety and Effectiveness	Additional information
Zhang et al. 2013 Repetitive transcranial magnetic stimulation for hallucination in schizophrenia spectrum disorders: A meta-analysis.	Systematic review and meta-analysis Included studies = 17 Included patients = 398.	Patients over 16 years. Patients with positive, negative and auditory hallucinations were not reported in this review. Diagnosis: AHRS, HSPSRS, PANSS, AHI, HCS.	TPC at left side with various frequencies, last for 1 to 4 weeks in 80% more and combined with pharmacotherapy. Studies vary on sessions from 4 to 9 sessions.	All sham controlled.	**Safety** Headache 7RCTs, n = 147, OR = 3.72, 95%CI = (1.32, 10.46) Facial muscle twitching 2RCTs, n = 64, OR = 15.5, 95%CI = (2.60, 92.72). **Effectiveness** AHS, MD = -0.42, 95%CI = (-0.54, -0.20), I^2 = 15%, Superior Response rate, OR = 2.94, 95% = (1.39, 6.24), I^2 = 0%, Superior.	PANSS+ and cognitive functions are not significantly different between the intervention and the comparator.

Author/Year/Title	Study profile	Population characteristics	Intervention rTMS Protocol	Comparator	Safety and Effectiveness	Additional information
Otani et al. 2015 A systematic review and meta-analysis of the use of repetitive transcranial magnetic stimulation for auditory hallucinations treatment in refractory schizophrenic patients	Systematic review and meta-analysis Included studies = 10 Included patients = 246	Mean age = 36.92 ± 2.82. Auditory hallucinations: All 10 studies included 246 patients with auditory hallucination. Diagnosis: 4 studies by HCS, 5 studies by AHRS and one studies by SAH. All patients are refractory schizophrenia.	TPC on the left side, and 80% or 90% intensity; Both high and low frequencies were adopted. All patients continued with pharmacotherapy.	All sham controlled except one RCT.	**Safety** No worsening cognitive functions. **Effectiveness** AHRS, HCS and SAH combined; SMD = 0.49, 95%CI = (0.11, 0.88), I^2 = 58.1%, Superior.	Refractory schizophrenia, defined as patients who have been treated with two different classes of antipsychotic drugs at an adequate dosage for the minimum period of 4 weeks each, without experiencing significant symptomatic relief
Hasan et al. 2016 Repetitive Non-invasive Brain Stimulation to Modulate Cognitive Functions in Schizophrenia: A Systematic Review of Primary and Secondary Outcomes.	Systematic review and meta-analysis Included studies = 33 Included patients = not reported.	Age not reported. Negative symptoms: PANSS- = Auditory hallucinations: 6 out of 33 studies included AH patients. Diagnosis: CANTAB.	Treatment protocols vary in the included studies. The primary protocol used PFC/DLPFC on the left side with high frequency and 80% more intensity.	9 out of 33 studies were sham controlled.	The study showed no superior effects for rTMS over sham stimulations in cognitive functions.	Also included open-labelled studies (6). This study focused on cognitive functions.

Author/Year/Title	Study profile	Population characteristics	Intervention rTMS Protocol	Comparator	Safety and Effectiveness	Additional information
Shi et al. 2014 Revisiting the therapeutic effect of rTMS on negative symptoms in schizophrenia: A meta-analysis.	Systematic review and meta-analysis. Included studies = 16 Included patients = not reported.	Adults without specific age limits. Negative symptoms: PANSS- = 12 studies score ranged from 14.85 to 32.61 on average. Diagnosis: DSM-III, III-R, IV or IV-TR, ICD9 and 10.	Treatment protocols vary in the included studies. A range of different locations were treated including left/right/bilateral DLPFC/PFC and left TPC. Duration was 1 to 4 weeks. 10 Hz left DLPFC at 110% intensity is the most common rTMS protocol.	Open-labelled studies were included.	PANSS- rTMS vs. sham, MD = 0.532, 95%CI = (0.191, 0.874), I2 = 51.22%, Superior.	Effect of rTMS tended to be poorer in patients with longer duration of illness (over 8 years).

Author/Year/Title	Study profile	Population characteristics	Intervention rTMS Protocol	Comparator	Safety and Effectiveness	Additional information
Dougall et al. 2015 Transcranial magnetic stimulation (TMS) for schizophrenia (Cochrane Review).	Systematic review and meta-analysis included studies = 41 Included patients = 1,473.	Age was not reported. Positive symptoms: PANSS+ = 11RCTs, n = 333. Negative symptoms measure by BPRS, PANSS and SANS scales Auditory hallucinations: 3 RCTs, n = 162 patients with AH. Diagnosis: DSM V.	Left PFC/DLPFC with a range of frequency (0.9Hz to 20 Hz). TBS TMS were also used. Included studies reported the use of first- and second-generation antipsychotics including clozapine and reiperidone.	All sham controlled. The review also compared rTMS to standard treatment (i.e. continuation with antipsychotics).	**Safety** Headaches (10RCT, n = 392, RR = 2.65, 95%CI = (1.56, 4.5)). Jaw and facial contraction (2 RCTs, n = 70, RR = 8.32, 95% CI = (1.13, 61.17)). **Effectiveness (TPC as the intervention)** CGI vs. sham, 7RCTs; n = 224, MD = -0.5, 95%CI = (-0.76, -0.23), I^2 = 44%, Superior. PANSS vs. sham, 4RCTs, n = 87, MD = -2.34, 95%CI = (-5.26, 0.59), I^2 = 0%, Non-inferior. PANSS+ vs. sham, 11RCTs, n = 333, MD = -1.24, 95%CI = (-3.15, -1.14), I^2 = 0%, Superior HCS vs. sham, 3RCTs, n = 162, MD = -1.64, 95%CI = (-1.97, -0.04), I^2 = 81%, Superior.	Cognitive states were reported in 3 studies using 39 different measures. Results were not significantly different. TPC vs. standard treatment was not significantly different for both safety and effectiveness. PFC over sham has significant improvement in depression score. TBS TMS over sham was significantly better regarding PANSS-score: 3 RCTs, n = 108, MD = -2.67, 95%CI = (-4.25, -1.09), I^2 = 0%.

Table 12: Characteristics of systematic reviews

Author / Year	Research focus	SR with RCTs	# studies included	Depression Types		Schizophrenia symptoms			Variability in TMS protocols	Comparators		TMS is effective	TMS is safe
				MDD	TRD	AH	+	-		Sham	Others		
Both depression and schizophrenia													
Enokibara et al. 2015	Both	✓	8	✓	NR				✓	✓		✓	✓
Hovington et al. 2013	Both	*	16	✓	✓	✓	✓	✓	✓	✓			✓
Kedzior et al. 2016	Both	✓	13	§	✓				✓			✓	
Kedzior et al. 2016	Both	✓†	13	§	✓		✓	✓	✓	✓			
Lefaucheur et al. 2014	Both	**	NR	NR	NR				✓			✓	
Radhu et al. 2013	Both	*	NR	✓	✓				✓			✓	✓
Slotema et al. 2009	Both	✓	40	NR	NR	✓		✓	✓	✓	✓		✓
Depression													
Allan et al. 2011	Depression	✓	31	✓	✓				✓	✓		✓	✓
Berlim et al. 2013	Depression	✓	6	✓	✓				✓	✓		✓	✓
Berlim et al. 2013	Depression	✓	7	✓	✓				✓	✓		✓	✓
Berlim et al. 2013	Depression	✓	10	✓	✓				✓	✓		✓	✓
Berlim et al. 2013	Depression	✓	7	✓	NR				✓				✓
Berlim et al. 2014	Depression	✓	29	✓	✓				✓	✓			✓
Brunoni et al. 2016	Depression	✓	81	✓	NR				✓	✓	✓		✓
Chen et al. 2017	Depression	✓	25	✓	✓				✓		✓		
Chen et al. 2017	Depression	✓	7	✓	NR				✓		✓		✓
Daskalakis et al. 2008	Depression	*	NR	NR	NR				✓				
Dell'Osso et al. 2011	Depression	✓	15	NR	NR				✓			✓	
Gaynes et al. 2014	Depression	✓	27	✓	✓				✓	✓			✓
Kedzior et al. 2014	Depression	✓†	54	§	✓				✓	✓		✓	✓

Author / Year	Research focus	SR with RCTs	# studies included	Depression Types		Schizophrenia symptoms			Variability in TMS protocols	Comparators		TMS is effective	TMS is safe
				MDD	TRD	AH	+	-		Sham	Others		
Kedzior et al. 2015	Depression	✓	19	✓	✓				✓				
Kedzior et al. 2015	Depression	✓	6	§	✓				✓	✓			✓
Kedzior et al. 2016	Depression	✓	16	✓	✓				✓	✓			✓
Lam et al. 2008	Depression	✓	32	✓	✓				✓	✓		✓	✓
Leggett et al. 2015	Depression	✓	73	✓	✓				✓	✓	✓	✓	✓
Liu et al. 2014	Depression	✓	7	NR	✓				✓	✓		✓	
MacQueen et al. 2016	Depression	✓	NR	✓	✓				✓	✓	✓		✓
Micallef-Trigona 2014	Depression	✓	9	§	✓				✓	✓	✓	✓	✓
MSAC 2014	Depression	✓	14	✓	✓				✓	✓	✓	✓	✓
Nakamura et al. 2007	Depression	✓	5	✓	✓				✓	✓			✓
Nordenskjold et al. 2016	Depression	✓	1	✓	✓				✓	✓		✓	✓
Perera et al. 2016	Depression	✓	24	§	✓				✓	✓			✓
Ren et al. 2014	Depression	✓	10	✓	✓				✓		✓	✓	✓
Schutter 2009	Depression	✓	30	✓	✓				✓	✓		✓	✓
Schutter 2010	Depression	✓	9	✓	✓				✓	✓		✓	✓
Serafini et al. 2015	Depression	✓†	10	✓	NR				✓	✓			✓
Silverstein et al. 2015	Depression	✓	41	§	✓				✓			✓	✓
Teng et al. 2017	Depression	✓	30	✓	✓				✓	✓		✓	✓
Tortella et al. 2014	Depression	✓	25	✓	✓				✓	✓			✓
Xie et al. 2013	Depression	✓	9	✓	✓				✓		✓	✓	✓
Zhang et al. 2015	Depression	✓	10	✓	✓				✓	✓		✓	✓
Schizophrenia													
Aleman 2007	Schizophrenia	✓	10			✓	✓	✓	✓	✓			✓
Arumugham et al. 2016	Schizophrenia	✓	54						✓				
Bunse et al. 2014	Schizophrenia	*	89						✓			✓	
Cole et al. 2015	Schizophrenia	✓	21			✓	✓	✓	✓	✓			✓
Cordes et al. 2006	Schizophrenia	✓	13			✓	✓	✓	✓	✓		✓	✓

Author / Year	Research focus	SR with RCTs	# studies included	Depression Types		Schizophrenia symptoms			Variability in TMS protocols	Comparators		TMS is effective	TMS is safe
				MDD	TRD	AH	+	-		Sham	Others		
Dlabac-de Lange et al. 2010	Schizophrenia	✓	10					✓	✓	✓			✓
Dougall et al. 2015	Schizophrenia	✓	41			✓	✓	✓	✓	✓			✓
Dougall et al. 2015	Schizophrenia	✓	41			✓	✓	✓	✓	✓			✓
Freitas et al. 2009	Schizophrenia	✓	47			✓	✓	✓	✓	✓			✓
Hasan et al. 2016	Schizophrenia	✓	33			✓			✓	✓	✓		✓
Montagne-Larmurier et al. 2011	Schizophrenia	✓	6			✓	✓	✓	✓	✓		✓	✓
Otani et al. 2014	Schizophrenia	✓	10			✓			✓	✓			✓
Poulet et al. 2010	Schizophrenia	✓	25			✓	✓	✓	✓	✓			✓
Prikryl et al. 2013	Schizophrenia	*	22					✓	✓	✓		✓	✓
Shi et al. 2014	Schizophrenia	✓	16					✓	✓	✓		✓	✓
Slotema et al. 2012	Schizophrenia	✓	17			✓	✓	✓	✓	✓			✓
Thomas et al. 2016	Schizophrenia	✓†	29			✓	✓	✓	✓	✓	✓	✓	✓
Tranulis et al. 2008	Schizophrenia	✓†	10			✓	✓	✓	✓	✓		✓	✓
Zhang et al. 2013	Schizophrenia	✓	17			✓	✓	✓	✓	✓			✓

Notes: * = umbrella reviews, ** = guidelines, † = reviews included studies not limited to RCTs; § = included patient with, but not limited to unipolar major depression
Not all the studies described in the PRISMA chart (Figure 1) were extracted in the tier-1 extraction. Eleven studies were further excluded from extraction and used for supporting evidence only.
Abbreviations: AH = auditory hallucinations; MDD = major depression disorder; NR = not reported; RCT = randomized controlled trial; SR = systematic review; TMS = transcranial magnetic stimulation; TRD = treatment resistant disorder ; + = positive symptom