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SUMMARY WITH CRITICAL APPRAISAL

Repetitive Transcranial Magnetic Stimulation for Patients with Depression: A Review of Clinical Effectiveness, Cost-Effectiveness and Guidelines – An Update

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Authors: Ron Pohar, Kelly Farrah

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Questions or requests for information about this report can be directed to Requests@CADTH.ca

Abbreviations

CANMAT	Canadian Network for Mood and Anxiety Treatments
CE	Cost-effectiveness
CND	Canadian dollars
DLPFC	Dorsolateral prefrontal cortex
ECT	Electroconvulsive therapy
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HDRS	Hamilton Depression Rating Scale
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
MADRS	Montgomery Asberg Depression Rating Scale
MDD	Major depressive disorder
PTSD	Post-traumatic stress disorder
QALY	Quality adjusted life year
RCT	Randomized controlled trial
rTMS	Repetitive transcranial magnetic stimulation
SGD	Singapore dollars
TRMD	Treatment resistant major depression
VA/DoD	Veterans Affairs and the Department of Defense
WTP	Willingness to pay

Context and Policy Issues

In Canada, based on 2012 survey data, the lifetime prevalence of major depressive disorder is 9.9% and the prevalence in the past year was 3.9%.[1] Major depressive disorder (MDD) is a condition that is particularly debilitating given the impact it has on social, emotional, physical, and cognitive functioning.[2] Treatment resistant major depression (TRMD) has been defined a number of different ways, but using the definition of failure to respond to at least two different classes of antidepressants, Canadian registry data suggests that 21.7% of individuals with MDD will have treatment resistant disease.[3]

Repetitive transcranial magnetic stimulation (rTMS) is a neurostimulation technique that uses a magnetic field to induce a strong and focused electrical current that is delivered to specific regions of the brain (e.g., the left pre-frontal cortex, over the left or right dorsolateral prefrontal cortex, or bilaterally over both cortices) with either a hand-held device or a helmet-shaped induction coil.[4] Repetitive transcranial magnetic stimulation (rTMS) delivers the electrical pulse in short bursts at a pre-set interval, with either high-frequency stimulation (5 to 20 Hz) or low-frequency stimulation (1 to 5 Hz).[4] The treatment is delivered in an outpatient setting, without the need for anesthesia. The mechanism by which rTMS may induce its effect in MDD is through inducing action potentials in the targeted brain region. Repeated electrical pulses cause changes in the synaptic connections in the specific target regions and increases or decreases the activity of target brain regions to normalize activity.[4]

Different regimens and protocols for rTMS have been studied but typically a therapeutic treatment course requires 20 to 30 sessions (typically five days per week) over a four-week to six-week time period.[4]

This report is an update to a previous CADTH Rapid Response on rTMS which was published in 2015.[5] The previous report included one health technology assessment, three meta-analyses, one systematic review, three randomized controlled trials (RCTs), and two cost-effectiveness analyses. The evidence identified mixed findings for the comparative efficacy of rTMS versus sham-treatment and similar comparative efficacy of rTMS versus pharmacotherapies. The cost-effectiveness analyses suggested that rTMS was dominant over pharmacotherapies and associated with an incremental cost-effectiveness ratio of C$75,844 relative to electro-convulsive therapy.

The objective of the current report is to provide an update regarding the clinical effectiveness and safety, cost-effectiveness, and guidelines for the use of repetitive transcranial magnetic stimulation for patients with treatment-resistant depression.

Research Questions

1. What is the clinical effectiveness and safety of repetitive transcranial magnetic stimulation for patients with treatment-resistant depression?
2. What is the cost-effectiveness of repetitive transcranial magnetic stimulation for patients with treatment-resistant depression?
3. What are the evidence-based guidelines regarding the use of repetitive transcranial magnetic stimulation for patients with treatment-resistant depression?

Key Findings

Three systematic reviews and five randomized controlled trials assessed the clinical effectiveness of repetitive transcranial magnetic stimulation for the management of treatment-resistant major depression. The rates of response to treatment and remission of symptoms were significantly greater with repetitive transcranial magnetic stimulation than sham treatment in all three systematic reviews, but significantly lower than with electroconvulsive therapy in the systematic review that included this comparator. One systematic review reported that repetitive transcranial magnetic stimulation was associated with a higher odds ratio for response than aripiprazole. The clinical relevance of the magnitude of the change in depressive symptoms in all studies was unclear. The cost-effectiveness evidence of repetitive transcranial magnetic stimulation was conflicting, but an analysis from the perspective of the Ontario healthcare system suggested repetitive transcranial magnetic stimulation was cost-effective relative to pharmacotherapy if the willingness to pay was greater than C$98,242 per quality adjusted life year. In contrast, electroconvulsive therapy was found to be cost-effective relative to repetitive transcranial magnetic stimulation if the willingness to pay was greater than C$37,640 per quality adjusted life year. One guideline provided a weak recommendation for repetitive transcranial magnetic stimulation for the management of treatment resistant major depressive disorder, but the level of evidence on which the recommendation was based was not reported. Another guideline recommended high-frequency repetitive transcranial magnetic stimulation to the left dorsolateral prefrontal cortex and low-frequency repetitive transcranial magnetic stimulation to the right dorsolateral prefrontal cortex as first-line options for individuals who failed to response to one antidepressant. The evidence supporting this recommendation was considered to be level one (i.e., the highest level).

Methods

Literature Search Methods

This report updates a literature search of a previous CADTH report.[5] A limited literature search was conducted by an information specialist on key resources including PubMed, PsycINFO the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were transcranial magnetic stimulation and depression. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized controlled trials, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between September 8, 2015 and May 30, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with treatment-resistant depression
Intervention	Repetitive transcranial magnetic stimulation
Comparator	Q1: Any active treatment, including electroconvulsive therapy Q2: Any active treatment, including electroconvulsive therapy Q3: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., onset of seizures, relapse /reoccurrence of depressive symptoms), safety, adverse events (e.g., scalp pain) Q2: Cost-effectiveness (cost per QALY, cost-benefit analysis) Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, economic evaluations, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to September 8, 2015. Guidelines with unclear methodology were also excluded. Randomized controlled trials that were captured in one or more of the included systematic reviews were not summarized separately (i.e., they were excluded from the report). Systematic reviews and meta-analyses with complete overlap (i.e., all relevant primary studies captured in another included systematic review) were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR (A MeaSurement Tool to Assess systematic Reviews) II checklist,[6] randomized studies were critically appraised using the SIGN 50 checklist,[7] economic studies were assessed using the Drummond checklist,[8] and guidelines were assessed with the AGREE (Appraisal of Guidelines for Research and Evaluation) II instrument.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 460 citations were identified in the literature search. Following screening of titles and abstracts, 390 citations were excluded and 70 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 59 publications were excluded for various reasons, and 13 publications met the inclusion criteria and were included in this report. These comprised three systematic reviews, five randomized controlled trials (RCTs), three economic evaluations, and two evidence-based guidelines. Appendix 1 presents the PRISMA[10] flowchart of the study selection. Three additional RCTs had met the selection criteria but were included in at least on systematic review, and were therefore not retained for this report.[11-13] As well, one systematic review was excluded due to complete overlap with another systematic review.[14]

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Three systematic reviews were selected for inclusion.[15-17] One systematic review was published in 2019, and included a literature search from database inception up to April 3, 2017.[15] Another systematic review was published in 2017 and included a literature search from 2003 to September 2014.[16] The third systematic review was published in 2016 and searched from January 1994 to March 1, 2015.[17] All three systematic reviews restricted inclusion to RCTs, with one systematic review including 23 RCTs,[15] one including 31 RCTs (12 of which assessed rTMS),[16] and one including 29 RCTs (Appendix 2, Table 2).[17] Overlap in relevant primary studies between systematic reviews is presented in Appendix 5.

Regarding primary studies, five RCTs were included, all of which were two-arm, sham-controlled, parallel-group, superiority studies.[18-22] Four studies were performed at a single centre,[18-22] and once was a multi-centre study(Appendix 2, Table 3).[21]

Three economic evaluations (all cost-effectiveness analyses) were included, two of which were described as Markov models[23,24] and one of which involved two separate decision analysis models.[25] The perspective was societal for one economic evaluation,[23] and that of the healthcare payer for the other two.[24,25] The time horizon was one year for two economic evaluations[23,24] and six months for the other.[25] All three economic evaluations compared rTMS with electroconvulsive therapy (ECT), but one also included a comparison to sham

treatment.[25] The cost inputs and key assumptions of each model can be found in Appendix 2, Table 4.

Two guidelines were included that addressed the use of rTMS in patients with TRMD, one from the Canadian Network for Mood and Anxiety Treatments (CANMAT)[26] and the other from Veterans Affairs and the Department of Defense (VA/DoD) in the United States.[27] Both guidelines were developed based upon systematic literature reviews, with no restrictions on study design. The CANMAT guideline formulated consensus-based recommendations based on the level of evidence (more information is provided in Appendix 2, Table 5). For the CANMAT guidelines, Level 1 evidence was a meta-analysis with narrow confidence intervals and/or two or more RCTs, with adequate sample size, preferably placebo controlled; Level 2 evidence was meta-analysis with wide confidence intervals and/or one or more RCTs with adequate sample size; Level 3 evidence was small-sample RCTs or nonrandomized, controlled prospective studies or case series or high-quality retrospective studies; and Level 4 evidence was expert opinion/consensus. The strength of recommendation was expressed in terms of lines of therapy as outlined in Appendix 2, Table 5.

For the VA/DoD Guideline, consensus-based recommendations were developed based on Grading of Recommendations, Assessment, Development and Evaluations (GRADE) evidence tables. Recommendations considered the level of confidence in the literature (Appendix 2, Table 5).

Country of Origin

Two systematic reviews were performed by authors from Canada[15,17] and one was performed by authors from the Netherlands.[16] One RCT was performed in Canada,[18] two in the United States,[19,21] one in Finland,[20] and one in South Korea.[22] The economic models considered inputs from Canada,[25] Singapore,[23] and Spain.[24] One guideline was Canadian[26] and the other was developed for use by Veterans Affairs and the Department of Defense in the United States (Appendix 2).[27]

Patient Population

All of the included systematic reviews selected studies with patients with unipolar TRMD, but did not specify inpatient or outpatient settings.[15-17] All excluded studies of patients with bipolar disorder. The definition of TRMD differed in the systematic reviews, with one of the three reviews[16] requiring patients to have failed to respond to two pharmacotherapy regimens of adequate dose and duration. The other two reviews did not specify a particular number of prior treatments required. Comorbidities and other clinical factors such as medication use were not reported in the three systematic reviews (Appendix 2, Table 2).

In the five RCTs, the definition of TRMD differed, but in all cases, participants had experienced failure to respond to at least one trial of an antidepressant.[18-22] All studies excluded patients with bipolar disorder and some forms of depression (e.g., depression with psychotic features). Patients with comorbid substance abuse were excluded from two studies.[20,22] Participants were generally on stable medications throughout treatment with rTMS (one study did not report on pharmacotherapy[22] and in one study, two patients were not on pharmacotherapy[19]). Four of the five RCTs enrolled patients of similar age (Appendix 2, Table 3, but differed in the proportion of male participants, ranging from 19% to 80.5%. The average age ranged from 36.8 to 65.0. One RCT enrolled only older adults aged 60 to 85.[18] One study (in veterans) included patients with post-traumatic stress

disorder (PTSD).[21] The number of participants in the trials was 21,[22] 40,[20] 40,[19] 52,[18] and 164 (Appendix 2, Table 3).[21]

All three economic evaluations based the base case on a population with TRMD. Two economic evaluations considered this to be failure to respond to two antidepressants.[23,25] The other economic evaluation considered a population who had severe depression and did not respond to pharmacological and psychological therapies (Appendix 2, Table 4).[24]

The CANMAT guideline addressed the use of neurostimulation techniques (including rTMS) in patients with unipolar MDD.[26] The target guideline users were all health care providers who care for this population. The section on rTMS was focused on TRMD.[26] The VA/DoD guideline addressed all interventions for the management of MDD, but included a section on rTMS in relation to TRMD. The guideline is intended for use by all health care providers who provide care to patients with MDD with a target population of all adult patients with MDD who receive care in VA/DoD settings (Appendix 2, Table 5).[27]

Interventions and Comparators

One systemic review considered rTMS applied unilaterally to the right or left dorsolateral prefrontal cortex (DLPFC) with at least 10 sessions;[15] one considered only the left DLPFC with at least 10 sessions,[17] and one did not specify the particular brain region but only stated rTMS.[16] The comparators included sham treatment in two of the systematic reviews,[15,17] and pharmacological comparators, ECT, and sham in the other, with no doses or frequencies specified (Appendix 2, Table 2).[16]

The protocols for rTMS delivery for the five included RCTs can be found in Appendix 2, Table 2. Four studies applied rTMS to the left DLPFC,[19-22] while one study applied rTMS bilaterally.[18] In two studies patients received 20 treatments over four weeks,[18,19] in one study patients received 30 treatments over six weeks,[20] in one study patients received 20 to 30 treatments in five session blocks,[21] and in one study patients received 10 treatments over two weeks.[22] All studies used a sham comparator procedure delivered with the same device (Appendix 2, Table 3).

The economic evaluations did not describe specific rTMS protocols, and had ECT as the comparator[23-25] or both ECT and sham treatment (Appendix 2, Table 4).[25]

The guidelines considered all rTMS protocols when evaluating the literature in order to make recommendations.[26,27] The CANMAT guidelines made recommendations specific to each protocol based on the available evidence for that protocol (Appendix 2, Table 5).[26]

Outcomes

For the systematic reviews, the outcomes considered included depressive symptoms expressed as mean change from baseline measured with a validated tool such as the Hamilton Depression Rating Scale (HDRS) or the Montgomery Asberg Depression Rating Scale (MADRS),[15,16] response or remission (which was defined at the individual study level and was typically based on HDRS scale scores),[15,17] and relapse.[17] Adverse events were reported in two systematic reviews.[16,17] One review reported that a difference of 3.5 units on the HDRS was a clinically important treatment effect.[17] A change of 1.6 to 1.9 units on the MADRS may be considered clinically relevant.[28] The length of follow-up was not specified for two of the systematic reviews, but appeared be the end of treatment in the primary studies.[15,17] For one systematic review, data were presented at multiple time points, but for

consistency with the other systematic reviews and primary RCTs, end of treatment data (i.e., six week data) are presented in the current report (Appendix 2, Table 2).[16]

The RCTs[18-22] also used depression rating scales (e.g., HDRS, MADRS) to measure change in symptoms and classify patients as having achieved response or remission. One trial measured other patient-reported outcomes including measures of anxiety, general function and work function.[19] One study (in veterans) measured symptoms of post-traumatic stress disorder (PTSD) to assess treatment impact.[21] Suicidal ideation and health-related quality of life (HRQL) were both assessed in two studies (Appendix 2, Table 3).[18,21]

All of the economic evaluations assessed quality adjusted life years gained (QALYs) and expressed results in terms of the incremental cost-effectiveness ratio (ICER).[23-25] Two studies obtained utility values from the literature,[24,25] and one from a hospital database.[23] One study also measured cost-effectiveness in terms of the cost per remission achieved (Appendix 2, Table 4).[23]

No outcomes were specified for either of the included guidelines.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

The strengths and limitations of the three included systematic reviews are summarized in Appendix 3, Table 6. All systematic reviews were based on comprehensive literature searches, spanning different time frames. One literature search excluded years prior to 2003, but this was rationalized as an attempted to reduce heterogeneity in the populations of the included studies.[16] All of the systematic reviews were restricted to RCTs only, without a rationale for this decision; however, this seems to be a reasonable decision given the potential for a placebo effect with treatment. The repeated contact with health care professionals on a daily basis to receive rTMS was noted as a potential factor that may complicate the ability to isolate the treatment effect of rTMS in some of the RCTs so the exclusion of less rigorous designs may be justified given the placebo response seen in clinical trials in MDD.[29] Risk of bias was assessed in the three systematic reviews using standardized tools (e.g., Cochrane Risk of Bias or the GRADE approach); however, it was unclear how the study quality was used to inform any analyses (i.e., it appeared to be for descriptive purposes only). Two of the systematic reviews did not provide sufficient detail on methods used for screening and data extraction.[15,16] The implications that this may have on the overall rigour and review findings is uncertain. Importantly, none of the included systematic reviews reported duplicate screening and data extraction. In terms of generalizability, the information provided on patient baseline characteristics was limited in the systematic reviews. However, two of the three systematic reviews[15,17] included all adult patients with TRMD, whereas one review restricted the enrollment to those that did not respond to two or more antidepressants.[16] The latter may be less in line with the CANMAT guidelines which suggest rTMS as a first-line treatment in patients who did not respond to one treatment.[26] Further, one systematic review considered all rTMS regimens pooled together,[16] which may not be appropriate given the potential for different efficacy depending on the protocol. Only one systematic review had pooled treatment effect estimates for rTMS versus ECT, so comparative efficacy to other active treatments, such as adjunctive pharmacotherapies for MDD, remains limited.[17] The longer-term effects of rTMS (both benefits and harms) beyond the end of treatment were not captured.

The key strengths and limitations of the five RCTs are summarized in Appendix 3, Table 7. In all studies, symptoms of depression were measured with the HDRS or MADRS, which are commonly used and recommended measures in clinical trials for MDD.[29] Randomization appeared to be appropriate in two trials,[18,21] but for the remaining trials, there were potential issues or lack of clarity with the manner in which randomization was performed,[19,20,22] or allocation was concealed,[20,22] and the outcome of randomization was a lack of balance in baseline characteristics in one RCT.[19] In one study, the rTMS group had HDRS and MADRS scores that would suggest more severe symptoms at baseline, however statistical comparisons were not conducted.[19] In most trials, the use of concomitant medications was balanced between groups, but in one trial, the rTMS group had a larger proportion of patients who were taking antidepressants and benzodiazepines at baseline.[18] For three trials, there were 20% or more patients who did not complete the trial or the number of completers could not be ascertained.[19-21] In four trials, patients who dropped out were excluded from the analyses, so intention-to-treat (ITT) analysis were not performed, making unclear if randomization was maintained.[18-20,22] Further, it was questionable if some of the trials had adequate power given the initial sample sizes, lack of power calculations, drop out, and non-statistically significant findings.[18-22] As well, for trials where it was stated that ITT analyses were used, it was unclear how the missing patients were included in the analysis (i.e., how values were obtained for drop-outs). In terms of generalizability, for all studies the specific rTMS protocol used was clearly described. Thus, the protocol can be compared to recommendations put forth in Canadian guidelines to determine applicability to practice. Three of the five RCTs enrolled patients who were refractory to only one antidepressant.[18,19,22] These populations are in alignment with Canadian practice guidelines.[26] The remaining two trials may still be generalizable to patients in Canada who have failed to respond to more lines of therapy.[20,21]

The critical appraisal of the economic evaluations is summarized in Appendix 3, Table 8. In the economic models, the methods used to obtain costs and the lack of discounting appeared to be appropriate given the time horizon. The cost estimates that were used as model parameters were presented clearly in cost tables.[23-25] The included costs appeared to be appropriate based on the stated perspective (e.g., indirect productivity costs were included in the model with a societal perspective).[23] The key limitation of the three economic evaluations was the time horizon of one year or less, which may not be realistic given that MDD can be a long-term condition. Two of the economic evaluations were from other countries,[23,24] so it is not clear if the results would be generalizable to Canada. The Canadian economic model used utility values that were not derived from a Canadian population.[25] It is not clear what impact that this would have on the overall estimated cost-effectiveness if Canadian utility data were available.

The critical appraisal of the included guidelines is summarized in Appendix 3, Table 9. The two guidelines met the majority of the checklist criteria for the AGREE II instrument (in particular with regards to rigour of development), with only minor limitations noted. Specifically, for the CANMAT guideline, there was limited representation of professional groups outside of psychiatry, pharmacy, and psychology,[26] whereas the VA/DoD guideline had much broader involvement including nursing, social work, and other medical specialties.[27] Neither guideline, however, sought the views of the target population. The CANMAT guideline was internally reviewed, but did not appear to have undergone external stakeholder review and did not have a clear process for updating the guideline.[26] That said, the guideline was an update to a previous 2009 guideline so it is possible that a procedure is, in fact, in place. The CANMAT guideline did not address applicability (i.e., barriers to implementation, resource implications, monitoring criteria, or tools). Similarly, the VA/DoD

guideline met the criteria for the “rigour of development” domain. Limitations included an unclear procedure for updating, but like the CANMAT guideline was an update to a previous guideline. It also included some monitoring parameters to considered and tools for implementation.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors’ conclusions.

Clinical Effectiveness of rTMS

There were three systematic reviews that assessed depressive symptoms, response and remission. These systematic reviews all selected only RCTs and had overlap in their included studies, as outlined in Appendix 4, Table 14. There were six studies included in all three systematic reviews and twelve additional studies included in two of the systematic reviews. The remaining 21 studies were included in one systematic review.

In one systematic review, the clinical effectiveness of unilateral rTMS and bilateral rTMS were assessed separately relative to sham treatment.[15] For unilateral rTMS, the weighted mean difference (WMD) in HDRS scores between rTMS and sham was 3.36 (95% confidence interval [CI], 1.85 to 4.88). When looking at subgroups of patients who used antidepressants concomitantly and patients who did not, the treatment effect was significant in both populations, but larger in combination with antidepressants (Appendix 4, Table 10). The rates of response and remission with unilateral rTMS were approximately twice that of the sham treatment. For bilateral rTMS, the WMD difference in HDRS scores between rTMS and sham was 2.67 (95% CI, 0.83 to 4.51), with response and remission rates that were 3.5 and 5.5 times higher, respectively (Appendix 4, Table 10).

A second systematic review, which did not separate unilateral and bilateral rTMS, found similar results. The difference in MADRS score was -3.6 points (95% credible interval [CrI], -7.6 to 0.3) between rTMS and sham, with the odds of response and remission being 8.01 (95% CrI, 1.16 to 56.98) and 8.58 (95% CrI, 1.15 to 112.55), respectively. The odds of response with rTMS relative to aripiprazole was 1.1 (95% CrI, 0.5 to 2.5). The withdrawal rate due to adverse events was four times higher with rTMS than with sham treatment (Appendix 4, Table 10).[16]

In the third included systematic review, the WMD in HDRS scores between rTMS and sham was 2.31 points (95% CI, 1.19 to 3.43, $P < 0.001$) in favour of rTMS. When looking at the treatment effect of rTMS according the frequency used (10 Hz or 20 Hz), the largest effect was seen in studies that used 20 Hz (WMD 4.96; 95% CI, 1.15 to 8.76). The risk difference in response and remission between rTMS and sham was 11% and 10%, respectively in favour of rTMS. For the comparison of rTMS to ECT, the WMD in HDRS scores was 5.97 (95% CI, 10.94 to 11.0) in favour of ECT, with a 72% higher response rate and 44% higher remission rate. The most commonly reported adverse events were headache and scalp discomfort with rTMS (Appendix 4, Table 10).[17]

Based on a 3.5 point clinical difference for the HDRS and approximately 2 point difference for the MADRS, the effect of rTMS would be considered clinically relevant in two systematic reviews, but not in the third.[17] The benefit of ECT over rTMS would also be considered clinically relevant. The authors of the three systematic reviews all concluded that there was some benefit associated with treatment with rTMS. This benefit was characterized as a “small, short-term effect” (p. 50),[17] “a moderate antidepressant effect” (p. 162),[15] and “significantly more efficacious than placebo/sham” (p. 706) (Appendix 4, Table 10).[16]

The five included RCTs produced conflicting results regarding the clinical effectiveness of rTMS (Appendix 4, Table 11). In one RCT, the difference in remission and response rates between rTMS and sham were statistically significant, in favour of rTMS.[18] This included only older adults. In three RCTs, differences in response and remission were statistically nonsignificant.[19-21] One study found a difference in treatment response, but not in remission between rTMS and sham.[22] When looking at the magnitude of change in HDRS scores (which was reported in two studies), no statistical differences were found and the magnitude of the difference in change was below the clinically important difference of 3.5 points.[19,21] When considering other endpoints, such as the HRQL, PTSD symptoms, suicidal ideation, anxiety, general functioning, and work functioning, differences between rTMS and sham were statistically nonsignificant.[18,19,21] Headache and pain were the most commonly reported adverse events with rTMS.[19,21] In one positive trial, the authors appropriately concluded that the findings demonstrated support for rTMS in late life depression.[18] However, all of the authors tended to make positive conclusions despite negative or conflicting trial findings. In two trials it was concluded that rTMS was effective in reducing symptoms despite statistically nonsignificant differences between rTMS and sham in improvement over baseline.[19,21] One study with conflicting results (with statistically nonsignificant effects for most outcomes) arrived at positive conclusions with regards to efficacy.[22] Finally, the authors of one study with negative findings emphasized the need to further investigate the placebo effect observed with the support provided in the rTMS setting.[20]

Cost Effectiveness of rTMS

There were three economic evaluations included in this Rapid Response report, all of which were based on modelling approaches (Appendix 4, Table 12). In comparison to ECT, rTMS was associated with lower costs and QALYs than ECT and was considered to be cost-effective relative to ECT in the inpatient setting based on an estimated Singapore dollars (SGD) 311,024 per QALY gained with ECT. If ECT could be performed in the outpatient setting, the cost per QALY gained was reduced to SGD 78,819. The willingness-to-pay (WTP) threshold was considered to be SGD 70,000 per QALY gained. Sensitivity analyses showed that the cost-effectiveness estimates were sensitive to changes in relative risk for remission between rTMS and ECT and cost for hospitalization due to ECT.[23]

Contrary to this finding, a Canadian cost-effectiveness analysis found the ICER per QALY gained with ECT to be C$37,641 relative to rTMS. One-way sensitivity analyses suggested that this result was robust, but most sensitive to changes in rate of ECT, rate of rTMS and the cost of rTMS (Appendix 4, Table 11). Based on probabilistic sensitivity analysis, at a 50,000 per QALY WTP threshold there was 45% chance that rTMS would be cost-effective, but a 20% chance at a $100,000 per QALY threshold. Relative to a sham treatment (i.e., background pharmacotherapy), rTMS was found to be cost-effective with an ICER per QALY of C$98, 242 (as long as the WTP threshold was greater than this number, i.e., $100,000).[25]

In the third cost-effectiveness analysis, rTMS was dominated by ECT in two different models based on different utility estimates (i.e., ECT had lower costs and higher QALYs) (Appendix 4, Table 11). Deterministic sensitivity analyses in which costs were varied showed little impact on the ICER, except in a scenario where acute rTMS treatment costs were 50% lower (or ECT costs 50% higher) then the ICER per QALY gained with ECT relative to rTMS would be around €40,000. The WTP threshold for interpreting cost-effectiveness was €30,000.[24]

Guidelines for Use of rTMS

Both of the included guidelines endorsed the use of rTMS in adult patients with TRMD (Appendix 4, Table 13). Specifically, the CANMAT guidelines consider rTMS as a first-line treatment for patients who have failed at least one antidepressant. This recommendation was based on Level 1 efficacy evidence and Level 3 safety evidence. Importantly, of the available protocols for rTMS, first-line options included high-frequency rTMS to left DLPFC and low-frequency rTMS to right DLPFC. Other protocols were considered second- and third-line alternatives.[26]

The VA/DoD guidelines for MDD simply suggest offering treatment with rTMS TRMD without endorsement of a specific protocol.[27] The evidence to support this recommendation was considered weak, which resulted in a weak recommendation in favour of (i.e., "weak for") rTMS for the management of TRMD.

Limitations

There were three systematic reviews and five RCTs included in this update that assessed the clinical efficacy of rTMS. While two of the systematic reviews did not report the overall quality of the included studies, one systematic review considered the evidence base to be moderate to high quality (based on GRADE). The additional five RCTs that were identified in the recent literature comprised a lower quality of evidence given issues with reporting of basic design features (randomization and allocation concealment), unclear reporting of statistical analyses, failure to follow the principles of ITT analysis, and differences between treatment arms at baseline. Drop-outs from the studies were also problematic, as was the limited reporting of adverse events. The potential for a placebo effect in clinical trials of MDD has been recognized, and given the rate of response in the sham group in some trials, this was a potential limitation. This, along with the drop-out rates, could impact the power of the trials, particularly given the initial study sample sizes. There did not appear to be major issues with the generalizability of the study protocols and selection of study participants given the definitions of TRMD used in the studies. The longer-term effects of rTMS (both benefits and harms) beyond the end of treatment were not captured in either the systematic reviews or RCTs.

Two of the economic evaluations may be limited by the use of foreign costing and sources for clinical estimates; however, it is important to note that a recent Canadian economic evaluation that appeared to be appropriately conducted was identified which is likely more generalizable than the other two. Other evidence of the cost-effectiveness of rTMS relative to ECT was conflicting, with one study suggesting that ECT was dominant over rTMS and the other suggesting rTMS was cost-effective relative to ECT. Generalizable Canadian clinical practice guidelines with minor limitations were identified which included recommendations for specific rTMS protocols. Thus, there appeared to be minimal gaps in the economic evidence and guidelines related to rTMS in Canada.

Conclusions and Implications for Decision or Policy Making

Three systematic reviews[15-17] and five RCTs assessed the clinical effectiveness of rTMS for the management of TRMD.[18-22] The rates of response to treatment and remission of symptoms were higher with rTMS than sham treatment in all three systematic reviews,[15-17] but higher with ECT in the systematic review that included this comparator.[17] One systematic review found higher odds of response with rTMS relative to aripiprazole, but this was only assessed following two weeks of treatment.[16] In terms of the magnitude of the

reduction in symptoms of depression, two of the three systematic reviews found a clinically relevant reduction in symptoms with rTMS relative to sham treatment and one systematic review found a clinically relevant reduction in symptoms with ECT relative rTMS.[15-17] At the individual study level, the five included RCTs produced inconsistent results.[18-22] In older adults, rTMS was associated with higher rates of response and remission than sham treatment,[18] and in one other RCT, rates of response (but not remission) were higher in rTMS than with sham treatment.[22] The remaining three trials did not find statistically significant differences between rTMS and sham treatment on these outcomes.[19-21] Further, the magnitude of the difference between the change from baseline in depressive symptoms was not clinically relevant. Further, the impact on other outcomes such as HRQL and anxiety was not statistically significantly different from sham treatment. The individual clinical trials had a number of important limitations including limited number of patients enrolled and incomplete follow-up which could have impacted the ability to find a difference. As well, the potential for a placebo effect with sham treatment (related to frequent contact with health care providers) could have limited the ability to find a difference between groups. Of note, a previous CADTH Rapid Response report[5] had similar findings, in that the efficacy of rTMS was found to be inconsistent relative to sham treatment and similar relative to pharmacotherapies. In general, however, taken at the systematic review level, the updated evidence would suggest some benefit in TRMD with rTMS compared to sham treatment.

The economic evidence included in this Rapid Response report from other countries (Spain and Singapore) was conflicting, with one suggesting that ECT was dominant over rTMS and the other suggesting rTMS was cost-effective relative to ECT for TRMD. However, the most relevant economic evaluation (performed from the perspective of the Ontario health care payer) found that rTMS would be cost-effective relative to pharmacotherapy if the WTP was greater than C$98,242 per QALY and that ECT would be cost-effective relative to rTMS if the WTP was greater than C$37,640 per QALY. The cost-effectiveness analysis included in a previous report also suggested that rTMS was dominant over pharmacotherapies.[5]

Further, the previous report found that ECT was associated with an incremental cost-effectiveness ratio of $75,844 (Australian dollars) relative to rTMS, which was higher than the current finding of an ICER of C$37, 641. An updated economic evaluation based on the more current literature may be needed to clarify the cost-effectiveness of rTMS relative to relevant treatments.

Two included guidelines, which appeared to be rigorous in their development, supported the use of rTMS in TRMD. The CANMAT guidelines endorsed particular protocols (high-frequency rTMS to left DLPFC and low-frequency rTMS to right DLPFC) as first-line options for individuals who failed to response to one antidepressant.

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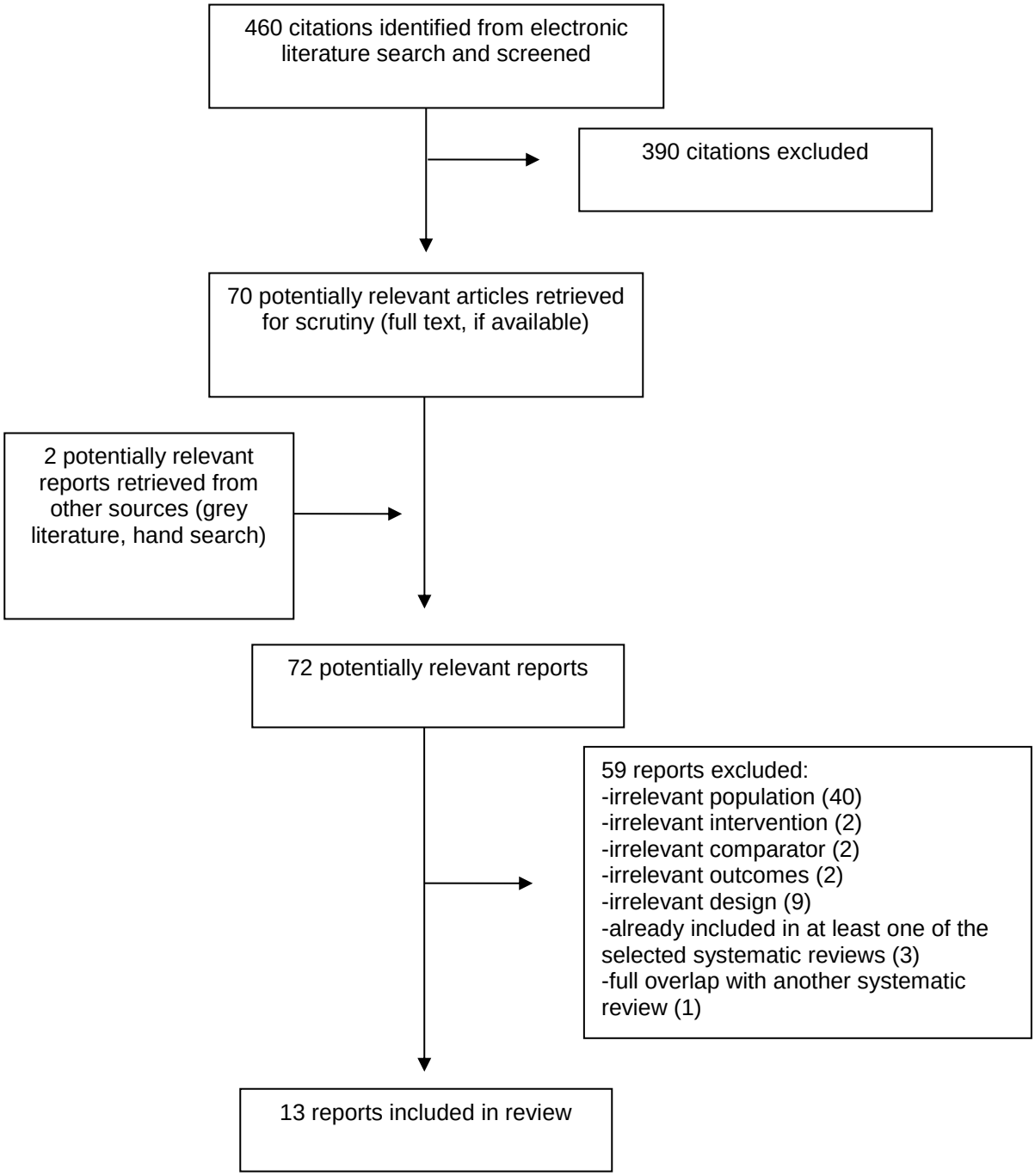
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Sehatzadeh 2019[15] **Canada**	The initial literature search was from inception up to Nov. 20, 2014 and updated up to Apr. 3, 2017. Inclusion restricted to RCTs. 23 RCTs included in total.	Adult patients with unipolar MDD who did not respond to treatment with antidepressant medications. Studies in which less than 20% of the sample had bipolar disorder were eligible for inclusion. Excluded depression due to specific conditions such as stroke, postpartum.	Interventions: Unilateral high-frequency applied to the left DLPFC Sequential bilateral low frequency rTMS applied to the right DLPFC Sequential bilateral high-frequency rTMS to the left DLPFC. One treatment per day for at least 10 sessions. Comparators: Not stated but appeared to be sham treatment from the included studies.	HDRS Response (50% reduction in symptoms) Remission (different definitions used across studies) Length of follow-up not specified, but appeared to be end of treatment.
Papadimitropoulou 2017[16] The Netherlands	The initial search of databases was from 2003 and to the date of search (October 21, 2013). An update was performed in September 2014. Inclusion restricted to RCTs. 31 RCTs included in total 19 of which assessed pharmacotherapy and 12 of which assessed ECT or rTMS.	Adult MDD patients who failed to respond to 2 antidepressant treatment regimens prescribed at adequate dose and duration. Mixed populations of TRD and MDD were excluded. Populations with bipolar disorder were excluded.	Interventions and comparators of interest were: SSRIs, SNRIs, TCAs, tetracyclic antidepressants, MAOIs, atypical antidepressants, antipsychotics, olanzapine/fluoxetine combination, adjunctive use of lithium, triiodothyronine, lamotrigine, ketamine, ECT and rTMS.	Depressive symptoms expressed in terms of change from baseline (in HDRS score). Multiple time points reported, but six-week data reported in this Rapid Response (i.e., end of treatment) for consistency with other SRs and the primary literature.

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Health Quality Ontario, 2016[17] Canada	The literature search was performed for RCTs published from January 1, 1994, to November 20, 2014. The search was updated on March 1, 2015. Inclusion restricted to RCTs. 29 RCTs included in total (23 in comparison to sham and 6 in comparison to ECT)	Adult patients with unipolar depression refractory to antidepressant medications. The study population had to include unipolar patients only or a proportion of bipolar patients ≤20% Studies in which at least 80% of patients were resistant to treatment were also included.	Interventions High-frequency rTMS (≥5 Hz) to the left dorsolateral prefrontal cortex and complied with rTMS safety guidelines. At least 10 sessions of rTMS treatment were required. Comparators: ECT or sham treatment	Remission rate Response rate Relapse rate; all based on scores from the HDRS Adverse events Length of follow-up not specified.

DLPFC = dorsolateral prefrontal cortex; ECT = Electroconvulsive therapy; HDRS = Hamilton Depression Rating Scale; MAOIs = Monoamine oxidase inhibitors; MDD = Major depressive disorder; RCT = randomized controlled trial; rTMS = Repetitive transcranial magnetic stimulation; SNRI = Serotonin noradrenaline reuptake inhibitor; SR = Systematic review; SSRI = Selective serotonin reuptake inhibitor; TCA = Tricyclic antidepressant; TRD = Treatment resistant depression.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Kaster 2018[18] Canada	Single-centre, prospective two-armed parallel superiority, RCT	Outpatients between the ages of 60-85 with a diagnosis of MDD. Current major depressive episode with a score ≥ 22 on the 24-item Hamilton Depression Rating Scale (HDRS-24). Lack of response to at least one adequate or two inadequate antidepressant trials during the current episode.	Intervention (n=25): rTMS with the Brainsway deep H1 coil device. Dose of rTMS: 18 Hz, at 120% RMT, 2 sec pulse train, 20 second inter-train interval, 167 trains, for a total of 6,012 pulses per session over 61 minutes applied to the dorsolateral and ventrolateral prefrontal cortex bilaterally. Comparator (n=27):	HDRS-24 used to define response and remission SSI BSI SF-36 4-week follow-up (end of treatment)

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Receiving stable dosages of psychotropic medications for at least four weeks prior to screening. Bipolar disorder and psychotic features excluded. Average age (SD) in Years: 65 (5.5) Male: 62%	Sham intervention with identical parameters, device and helmet but the active H1 coil was disabled, and sham H1 coil located within the treatment helmet but far above the participant's scalp was activated to produce the same sensation. Both intervention and comparator were administered five days per week for a total of 20 treatments over 4 weeks.	
Taylor 2018[19] United states	Single-centre prospective two-armed parallel superiority, RCT	Outpatients with MDD between the ages of 22 to 65 years old. Failed at least one trial of antidepressant medication, severity of moderate defined as MADRS ≥18 and ≤ 5 years in the current episode. Bipolar disorder, PTSD, OCD, psychotic features excluded. All patients but two were on antidepressant medications. Average Age (SD) in Years): rTMS, 46.9 (10.7); Sham, 44.13 (11.1) Male: 34%	Intervention (n=20): rTMS delivered at 10 Hz frequency at 120% of motor threshold and 3000 pulses/session to the left dlPFC, determined by individualized neuronavigation. Comparator (n=20): Sham treatment delivered with a sham coil was identical in shape and weight to the active coil, but did not deliver any magnetic energy. Both intervention and comparator were administered five days per week for a total of 20 treatments.	MADRS HDRS QIDS-SR GAD assessment Work and Social Adjustment Scale Global Assessment of Function End of treatment (4 weeks)

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Valkonen-Korhonen, 2018[20] Finland	Single-centre prospective two-armed parallel superiority, RCT	Adult patients with a diagnosis of TRMD defined as a poor or unsatisfactory response to at least two antidepressive medications used for at least six weeks with a dose equivalent to 150 mg of imipramine. No specific severity was required for enrollment but all patients had a current episode of MDD and ongoing medication for depression. Bipolar disorder, substance abuse, psychotic features excluded. Male: 46% Average Age (SD) in Years: 36.8 (not reported)	Intervention (n=20): Active bifrontal rTMS (10 Hz rTMS on left DLPFC and 1 Hz rTMS on right DLPFC) delivered with the Magstim Rapid2 Stimulator. Comparator (n=20): bilateral sham rTMS delivered with an externally identical sham coil. Both groups received 30 sessions in total (5 sessions per week for 6 weeks)	HDRS MADRS End of treatment (six weeks)
Yesavage, 2018[21] United States	Multi-centre prospective two-armed parallel superiority, RCT	Adult veterans with a diagnosis of TRMD, which required the failure of an adequate trial of at least 2 prior pharmacologic interventions. Had to be stable on medications for 4 weeks prior to randomization and continue receiving concomitant medications throughout rTMS treatment.	Intervention (n=81): Left prefrontal rTMS treatment (10 Hz, 120% motor threshold, 4000 pulses/ session) delivered with a modified MagPro R30 (MagVenture) device with Cool-B65-A/P coil that had an active and placebo side. Comparator (n=83): Sham (control) rTMS treatment. The P (placebo) side of the coil delivered sham treatment.	Remission on HDRS MADRS Beck Depression Inventory-II PTSD Checklist–Military Clinician-Administered PTSD Scale Beck Scale for Suicide Ideation

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Veterans with comorbid PTSD and a history of substance use disorders were included. Male: 80.5% Average Age (SD) in Years: 55.2 (12.4)	Both groups received between 20 and 30 sessions of rTMS delivered in 5 session blocks over a period of 5 to 12 calendar days. Those with remission after the initial 20 to 30 sessions had 6 additional taper sessions that were delivered over a 3-week period.	Columbia Suicide Severity Rating Scale Veterans RAND 36-item Health Survey Measured at end of 24-week follow-up period.
Kang 2016[22] South Korea	Single-centre prospective two-armed parallel superiority, RCT	Adults aged 20 to 75 with TRMD which was defined as failure to have adequate improvement after an 8-week trial of SSRI. Patients with anxiety, psychotic, substance use disorders or any other form of depressive disorder other than MDD were excluded. Male: 19% Average Age (SD) in: rTMS= 42.8 (19.1); Sham= 52.2 (20.1)	Intervention (n=12): rTMS delivered with a Magstim Rapid Stimulator over the to the left DLPFC (10 Hz for 5 seconds per train and 20 trains with an intertrain interval of 25 seconds for 10 minutes, 110% motor threshold, 1000 pulses/ session). Comparator (n=9): Sham (control) rTMS treatment with an identical coil that made the same scalp sensations and sounds as the active coil. Both groups received 10 sessions over a two-week period.	HRDS

BSI = Beck Scale for Suicide Ideation; DLPFC = dorsolateral prefrontal cortex; ECT = Electroconvulsive therapy; GAD-A = Generalized Anxiety Disorder Assessment; HDRS = Hamilton Depression Rating Scale; MAOIs = Monoamine oxidase inhibitors; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = Major depressive disorder; OCD = Obsessive compulsive disorder; PTSD = Post-traumatic stress disorder; QIDQ = Quick Inventory of Depressive Symptoms; RCT = Randomized controlled trial; RMT = Resting motor threshold; rTMS = Repetitive transcranial magnetic stimulation; SD = Standard deviation; SF-36 = 36-Item Short Form Survey; SNRI = Serotonin noradrenaline reuptake inhibitor; SSI = Scale for Suicidal Ideation; SSRI = Selective serotonin reuptake inhibitor; TCA = Tricyclic antidepressant; TRD = Treatment resistant depression; TRMD = Treatment resistant major depression.

Table 4: Characteristics of Included Economic Evaluations

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Zhao, 2018[23] Singapore	Cost-effectiveness analysis with a one-year time horizon, and a Singapore societal perspective.	To evaluate the cost-effectiveness of rTMS and ECT for patients with TRD in the inpatient and outpatient setting.	Patients with an acute episode of TRD (failure to respond to two antidepressants).	rTMS compared with ECT	Model-based approach with probabilistic and deterministic sensitivity analyses. A state transition Markov model was used.	Estimates were based on the local treatment algorithm and distribution of uptake for all other possible options after failing the preceding treatment modality. Performed a SR and MA to calculate treatment effect estimates. Performed hospital database analysis to determine estimates of quality of life and remission rates. Direct costs: treatment cost of rTMS and ECT, cost for monitoring,	Received either 24 rTMS or 12 ECT sessions for a period of one month. Willingness-to-pay threshold of SGD 70,000 per QALY gained (one gross domestic product per capita in Singapore in 2015). Assumed that absenteeism during the course of treatment with ECT and rTMS to be 20 and 6 days, respectively.

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
						hospitalization and managing patients with remission, non-remission, and relapse. Indirect costs: loss of productivity such as absenteeism while seeking treatment. Costs were from a hospital database.	
Health Quality Ontario, 2016[25] Canada	Cost-effectiveness analysis, with a six-month time horizon from the Ontario health care payer perspective.	To estimate the cost-effectiveness of rTMS versus ECT and standard care (sham) for patients who have TRD and are willing to undergo treatment.	Patients diagnosed with MDD who have failed to benefit from two or more antidepressant treatments and whose disease is thus considered treatment resistant. Patients in the economic models were 1) eligible for and willing to be given ECT or rTMS or 2) patients who refuse ECT	rTMS compared with ECT or sham (for those not eligible for ECT)	Two separate decision analysis models.	Response and remission rates were taken from a systematic review conducted internally. Utility values were taken from the literature. Cost estimates were taken	TRD patients who did not respond to an initial treatment would continue with sham rTMS for the rest of the cycle Patients who achieved remission or continued to respond after the initial treatment would remain in remission or as

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
			because of intolerance or medical reasons.			from the literature, internal sources, and expert opinion. Costs included hospital admission, medication, and physician visits.	responders to the treatment for the rest of the treatment cycle.
Vallejo-Torres, 2015[24] Spain	Cost-effectiveness analysis, with a one-year time horizon from the perspective of the National Health Service.	To develop a decision analytical model of the cost-effectiveness of ECT vs. rTMS for treatment-resistant severe depression	Patients with severe depression who do not respond to pharmacological and psychological therapies.	rTMS compared with ECT.	Markov model-based approach with deterministic sensitivity analyses.	Transition probabilities between states for ECT and rTMS (and associated relative risks) were taken from the literature. Use of healthcare resources the unit costs of health care resources were taken from the literature and expert opinion.	The values in the model for patients with ECT would be the same as for patients with rTMS. Transition probabilities and relative risks which were reported for a different time period were converted to instantaneous rates assuming a fixed rate and then probabilities for a 15-day period.

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
						Utility weights for the health states were taken from the literature.	

ECT = Electroconvulsive therapy; rTMS = Repetitive transcranial magnetic stimulation; SGD = Singapore Dollars; TRD = Treatment resistant depression.

Table 5: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
CANMAT 2016[26]						
Intended Users: Health care professionals (psychiatrists and mental health professionals) who provide care to adults with unipolar major depressive disorder Target Population: Adults with unipolar major depressive disorder	Neurostimulation Treatments, including rTMS	Not stated specifically but efficacy and safety	Update of 2009 guidelines. Systematic review of multiple databases to identify literature. Expert panels were established for each guideline section with content experts from psychiatry, pharmacy, and psychology.	The evidence was graded using level of evidence criteria from the previous guidelines Level 1 Meta-analysis with narrow confidence intervals and/or 2 or more randomized controlled trials (RCTs) with adequate sample size, preferably placebo controlled Level 2	Based on systematic review with consideration given to expert opinion and consensus. Strength of recommendations expressed as lines of treatment according to strength of evidence: First line Level 1 or Level 2 Evidence, plus clinical support Second line	Manuscript drafts were circulated for discussion and consensus. If consensus could not be reached, a dissenting statement could be submitted for consideration. Final manuscripts were approved by all coauthors.

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
			Evidence tables created for purposes of grading evidence.	Meta-analysis with wide confidence intervals and/or 1 or more RCTs with adequate sample size Level 3 Small-sample RCTs or nonrandomized, controlled prospective studies or case series or high-quality retrospective studies Level 4 Expert opinion/consensus	Level 3 Evidence or higher, plus clinical support Third line Level 4 Evidence or higher, plus clinical support	
Veterans Affairs/Department of Defense, 2016[27]						
Intended Users: all healthcare professionals who treat patients for MDD. Target Population: Adults with MDD being treated in any VA/DoD clinical setting including those newly	Pharmacotherapy, psychotherapies, and somatic therapies for MDD, including rTMS and other neurostimulation techniques.	Improvement in quality of life and social and occupational functioning Improvement of symptoms Retention (keeping patients engaged in treatment) Improvement in co-occurring conditions	Process involved: Formulating evidence questions (key questions) A systematic review involving multiple databases was used to select the evidence according to	The GRADE methodology was used to assess the quality of the evidence base. The confidence in the quality of the evidence was determined by a Work Group that reflected the quality of the evidence base and the certainty	Recommendations were formulated at a face-to-face meeting with CPG Champions and Work Group members GRADE methodology was used to assign a grade for the strength for each recommendation (no further description provided).	The draft of the guidelines was sent out for peer review and comment. The guideline was peer-reviewed by individuals working within the VA and DoD health systems and external experts from

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
diagnosed, those receiving ongoing treatment and those with chronic depression.		Reduced mortality Prevention of recurrence or relapse	prespecified criteria. Systematic review was performed by ECRI.	in that evidence (the methodological quality of the studies for each outcome variable). Confidence was assigned a rate of "High," "Moderate," "Low," or "Very Low."		relevant outside organizations: American Psychiatric Association Academic experts

CPG = Clinical practice guidelines; DoD = Department of Defense; ECT = Electroconvulsive therapy; ECR I= Emergency Care Research Institute; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; MDD = Major depressive disorder; RCT = Randomized controlled trial; rTMS = Repetitive transcranial magnetic stimulation; VA = Veterans Affairs.

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR II Checklist[6]

Strengths	Limitations
Sehatzadeh 2019[15]	
The authors stated that the review was conducted according to an a priori protocol, but no further details of the protocol were provided. The literature search strategy appeared to be comprehensive (searching multiple databases). Study quality was assessed using the GRADE approach. The authors had no funding sources or conflict of interest. Sensitivity analyses were performed for the meta-analysis based on the time period in which the study was performed, but it was unclear if this was planned a priori.	The PICOs of the review were clearly stated with the exception of the comparator, which appeared to be sham given that all included studies were rTMS compared with sham. Only RCTs were included in the systematic review. There was no rationale provided for this decision. There was no description of whether the study selection and data extraction were performed in duplicate. There was no list of excluded studies provided. The funding source of the included studies was not reported in the review. There was no rationale provided for the meta-analysis and publication bias was not assessed.
Papadimitropoulou 2017[16]	
The PICOs and research question were clearly presented. The PICOs were detailed and unambiguous in the supplemental materials. The literature search appeared to be comprehensive, but only went back to 2003. This was justified as a means of reducing heterogeneity between studies. Study selection was performed in duplicate. The Cochrane Risk of Bias Tool was used to assess study quality. The statistical methods for the review appeared to be appropriate.	The authors did not state that the review was conducted according to an a priori protocol. Methods for data extraction were unclear. There was no list of excluded studies. The funding source of the included studies was not reported in the review. Publication bias was not assessed. Limited study characteristics were available in the supplemental materials.
Health Quality Ontario, 2016[17]	
The PICOs and research question were clearly presented. The PICOs were detailed and unambiguous. The literature search strategy appeared to be comprehensive (searching multiple databases).	The authors did not state that the review was conducted according to an a priori protocol. Only RCTs were included in the systematic review. There was no rationale provided for this decision. The procedures for screening and data extraction were not explained in the report.

Strengths	Limitations
The included studies were described in adequate detail with regards to rTMS protocols, definitions of study outcomes, and characteristics of the study populations. Risk of bias was assessed using GRADE approach. The statistical analysis using random effects models was chosen a priori and appeared to be justified. Sensitivity analyses were performed based on treatment effect precision and by rTMS protocol to explore heterogeneity. Publication bias was assessed using funnel plots.	There were no lists of included and excluded studies provided. There was no report of funding source for the included studies or conflict of interest for the authors.

GRADE = Grading of Recommendations, Assessment, Development and Evaluations; PICOs = Population, Intervention, Comparator, Outcome; RCT = Randomized controlled trial; rTMS = Repetitive transcranial magnetic stimulation.

Table 7: Strengths and Limitations of Clinical Studies using the SIGN 50 Checklist for Randomized Controlled Trials[7]

Strengths	Limitations
Kaster, 2018[18]	
The study addressed an appropriate and clearly focused question. All relevant outcomes were measured in a standard, valid and reliable way using standardized, validated scales. The assignment to the order of treatments was random and the method of randomization was described as a permuted block method with a random number generator prepared by an independent study consultant. Follow-up was more than 80% complete; some patients could not be analyzed because the coil used was changed after 6 patients experienced adverse events. The patients were asked to identify the treatment; failure to do so accurately suggests the blinding was maintained. In both groups all patients were on background medication.	The method of allocation concealment was not described. All subjects were not analyzed in the groups to which they were randomly allocated (intention to treat analysis). • An intention to treat analysis was not performed as the initial six patients randomized were removed from the analysis. The treatment and control groups were not similar at the start of the trial. • The rTMS group had a larger proportion of patients on antidepressants and benzodiazepines at baseline (not tested statistically).
Taylor, 2018[19]	
The study addressed an appropriate and clearly focused question. All relevant outcomes were measured in a standard, valid and reliable way using standardized, validated scales. In both groups almost all patients (except 2) were on background medication.	The assignment of subjects to treatment groups was randomized. • Patients were assigned to treatment arm, using block randomization, stratified by gender. However, a study team member performed the randomization so it was unclear if the blinding was truly maintained or allocation concealed.

Strengths	Limitations
	• There were issues with the randomization in that the individuals in the rTMS group had more severe depression based on MADRS and HDRS-17 scores at baseline. Follow-up was available for exactly 80% of the patients, so loss to follow-up could have been an issue particularly with power given the limited sample size to begin with and nonstatistically significant study findings for all outcomes. The authors did not use an intention to treat analysis so it was unclear if randomization was maintained. The analysis was based on the available patients.
Valkonen-Korhonen, 2018[20]	
The study addressed an appropriate and clearly focused question with a clear definition of TRMD based on Finnish guidelines. All relevant outcomes were measured in a standard, valid and reliable way using standardized, validated scales. In both groups all patients were on background medication.	The assignment of subjects to treatment groups was randomized. • Patients were randomly allocated to active and sham rTMS groups using a series of envelopes that were shuffled and numbered. • It is not clear how well this would work in terms of shuffling thoroughly or whether allocation would be concealed (e.g., it did not state that the envelopes were opaque). The percent of patients that dropped out was completely unclear. No denominators were presented for the data analysis, nor was there a study flow sheet but possibly 85% complete based on some numbers available in the text. The statistical analysis was very poorly reported, with no data tables and simply the number of patients who achieved the outcomes. There were no denominators presented. It was not clear if the analysis was based on the intention to treat principle. There was a large placebo effect which made the study difficult to interpret.
Yesavage, 2018[21]	
The study question was clear and focused with a clear definition of the population and intervention to be assessed. The assignment of subjects to treatment groups was randomized using an adaptive randomization scheme based on a coin. • All patients and study staff were blinded to randomization. Allocation was concealed by study staff key-entering an assigned patient number into the rTMS device to deliver the appropriate treatment (active or sham) for each participant.	The study results were not analyzed according to site so it was uncertain if the results were comparable across sites. 76% of randomized patients completed the study. It was not clear how missing data were handled to create the ITT data set which included all participants. In both groups all patients were on background medication, but suicidal Ideation and Beck Depression Index scores were higher at baseline in the sham group (not tested statistically).

Strengths	Limitations
All relevant outcomes are measured in a standard, valid and reliable way using standardized, validated scales. An intention to treat analysis was performed.	
Kang 2016[22]	
The study question was clear and focused with a clear definition of the population and intervention to be assessed. All relevant outcomes were measured in a standard, valid and reliable way using standardized, validated scales.	The randomization was described as stratified by age, gender, and severity of depression. The method of randomization was not described and it is not clear if stratification by this number of factors could work given that only 21 patients were included. • The method of allocation concealment was not described. Clinicians administering the treatments were not blinded to group assignment. It was not clear if this could compromise the blinding overall. 75% of randomized patients completed the study. The analysis was based only on completers so it was not clear that randomization would be maintained. The analysis did not follow the intention to treat principle and the results of the statistical analysis were difficult to understand given the lack of presentation of the difference between groups in the change from baseline. This made the clinical relevance of the improvement difficult to interpret. The groups did not appear to be balanced with regards to baseline characteristics and it was unclear if the patients were on background pharmacotherapy.

HDRS = Hamilton Depression Rating Scale; ITT = Intention to treat; MADRS = Montgomery–Åsberg Depression Rating Scale; rTMS = Repetitive transcranial magnetic stimulation.

Table 8: Strengths and Limitations of Economic Studies using the Drummond Checklist[8]

Strengths	Limitations
Zhao, 2018[23]	
The research question, its importance, the rationale for selecting the intervention and comparator, and rationale for type of economic model were all clearly stated. The estimated treatment effects were derived from a systematic review and meta-analysis, the methods for which were described. Health care cost and utility (HRQL) data sources were clear.	The time horizon of the model was one year, which may not be realistic but the authors rationalized this choice based on limited long-term data. The costs were not discounted (which was likely appropriate given the time horizon), but there was no rationale provided for this decision.

Strengths	Limitations
The source of cost data and specific costs included were clearly presented. The rationale for including productivity costs was provided.	Sensitivity analyses were described in the methods, but the results were not presented and the parameters that were varied in these analyses was not clear, nor was the range used. There was no description of the populations from which the model parameters were derived. The generalizability of the cost and utility estimates to Canada is unclear.
Health Quality Ontario, 2016[25]	
The research question, its importance, the rationale for selecting the intervention and comparator, and rationale for type of economic model were all clearly stated. The estimated treatment effects were derived from a systematic review and meta-analysis, the methods for which were described in an appendix to the report. The source of cost data and specific costs included were clearly presented. The rationale for the time horizon and discount rate (i.e., no discounting given the six-month time horizon) were provided. Sensitivity analyses were described in the methods, including the parameters that were varied and the ranges used. Details of currency valuation (i.e., 2014 Canadian dollars was provided).	Health care cost and utility (HRQL) data sources were clear but it was uncertain if the utilities used would be generalizable to Canada. The perspective used was only that of the Ontario Ministry of Health, so no indirect costs were captured.
Vallejo-Torres, 2015[24]	
The research question, its importance, the rationale for selecting the intervention and comparator, and rationale for type of economic model were all clearly stated. Sensitivity analyses were described in the methods, including the parameters that were varied and the ranges used. The currency valuation was described. Cost data and specific costs included were clearly presented and the source of the data was clear.	The estimated treatment effects were derived from meta-analysis, but no methodology was provided. There was no rationale for the time horizon and discount rate (i.e., no discounting given the one-year time horizon) provided. The utility values were considered uncertain (but were included as a parameter in the sensitivity analysis). Unit costs are specific to Spain so generalizability to Canada is uncertain.

Table 9: Strengths and Limitations of Guidelines using AGREE II[9]

Item	Guideline	
	CANMAT, 2016[26]	Veterans Affairs/Department of Defense, 2016[27]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	No. Some groups not represented such as nursing or social work.	Yes, included psychiatry, psychology, nursing, pharmacy, social work, family medicine, internal medicine, emergency medicine, and mental and behavioral healthcare.
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No	No
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	Yes. Multiple database searches.	Yes. Multiple database searches.
8. The criteria for selecting the evidence are clearly described.	Unclear process for literature selection.	Process not clearly described but referenced to standard methods for VA/DoD guidelines.
9. The strengths and limitations of the body of evidence are clearly described.	Yes. Created evidence tables and graded literature.	Yes. Created evidence tables and graded literature.
10. The methods for formulating the recommendations are clearly described.	Yes. Process for evidence consideration, reaching consensus described.	Yes. Standard processes used and clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes. Both evidence of safety and efficacy graded.	Yes. Both evidence of safety and efficacy were considered.
12. There is an explicit link between the recommendations and the supporting evidence.	Yes. Presented levels of evidence tied to strength of recommendation.	Yes. Confidence ratings and strength of recommendations provided for most.
13. The guideline has been externally reviewed by experts prior to its publication.	No. Appears to have only undergone internal review.	Yes. Internal and external peer review procedures.
14. A procedure for updating the guideline is provided.	No	No
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes

Item	Guideline	
	CANMAT, 2016[26]	Veterans Affairs/Department of Defense, 2016[27]
16. The different options for management of the condition or health issue are clearly presented.	Yes. Covered six different types of neurostimulation.	Yes. Pharmacotherapy, psychotherapies, and somatic therapies are all evaluated
17. Key recommendations are easily identifiable.	Yes. Presented in tables.	Yes. Numbered recommendations are provided in text at the beginning of each section.
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	No	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No	Yes. A set of guideline toolkit materials were produced.
20. The potential resource implications of applying the recommendations have been considered.	No	Unclear
21. The guideline presents monitoring and/or auditing criteria.	No	Some monitoring parameters were included, but not for rTMS.
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Yes. Does not appear to have influence.	Yes. Does not appear to have influence.
23. Competing interests of guideline development group members have been recorded and addressed.	Yes. Conflict of interest declared.	Yes. Conflict of interest declared.

CANMAT = Canadian Network for Mood and Anxiety Treatments; rTMS = Repetitive transcranial magnetic stimulation; VA/DoD= Veterans Affairs/Department of Defense.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 10: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Sehatzadeh, 2019[15]	
Unilateral rTMS versus sham treatment *HDRS Difference in Change from Baseline* (n=18 studies) Overall WMD 3.36 (95% CI, 1.85 to 4.88, I^2 = 62.4%) With concomitant use of antidepressants WMD 3.64 (95% CI, 1.52 to 5.76, I^2 = 69.6%) Without concomitant use of antidepressants WMD 2.47 (95% CI, 0.90 to 4.05, I^2 = 15.3%) Overall Pooled Rate Ratio Response (n=17) 2.00 (95% CI, 1.26 to 3.19, I 2 = 50.4%) Overall Pooled Rate Ratio Remission (n=13) 2.33 (95% CI, 1.52 to 3.58, I 2 = 0%) **Bilateral rTMS versus sham treatment** Overall HDRS Difference in Change from Baseline (n=4 studies)[A] WMD 2.67 (95% CI, 0.83 to 4.51, I^2 = 0%)[B] Overall Pooled Rate Ratio Response (n=7) 3.55 (95% CI, 1.87 to 6.76, I^2 = 0%) Overall Pooled Rate Ratio Remission (n=6) 5.54 (95% CI, 1.96 to 15.61, I^2 = 0%)	*"Our study suggests that rTMS has moderate antidepressant effects and appears to be promising in the short-term treatment of patients with unipolar TRD. However, it is not clear from this study whether the effects are sustained over time without using maintenance treatment."* P. 162
Papadimitropoulou, 2017[16]	
2 Week Data vs. Aripiprazole **Response Rate – Odds Ratio** 1.1 (95% CrI, 0.5 to 2.5) **6 Week Data vs. Sham** MADRS Score – Difference in Change from Baseline versus Placebo/Sham (Number of studies unclear) -3.6 (95% CrI, -7.6 to 0.3) Response Rate – rTMS versus Placebo/Sham OR 8.01 (95% CrI, 1.16 to 56.98) Remission Rate – rTMS versus Placebo/Sham OR 8.58 (95% CrI, 1.15 to 112.55)	*"Pooled intensities of rTMS were found to be significantly more efficacious than placebo/sham throughout all analyses and numerically better than most pharmacological comparators with the exception of ketamine at 2 weeks."* P. 706

Main Study Findings	Authors' Conclusion
Adverse Events rTMS had a four-fold increase in withdrawal due to adverse events relative to placebo/sham	
Health Quality Ontario, 2016[17]	
rTMS versus Sham (n=15) HDRS Difference in Change from Baseline WMD 2.31 points (95% CI, 1.19 to 3.43, *P* < 0.001 favouring rTMS; I^2 = 19.8%) **Subgroups for** HDRS Difference in Change from Baseline *Frequency of 20 Hz* WMD 4.96 (95% CI, 1.15 to 8.76) *Frequency of 10 Hz* WMD 1.93 (95% CI, 0.74 to 3.12) *Frequency < 10 Hz* WMD 2.03 (95% CI, -2.07 to 6.12) Risk Difference – Response 0.11 (95% CI, 0.03 to 0.18; I^2 = 65.6%), indicating 11% increase in response rate comparing rTMS with sham rTMS. Risk Difference – Remission 0.10 (95% CI, 0.03 to 0.17; I^2 = 56.1%), indicating a 10% increase in remission rate favouring rTMS over sham rTMS. **rTMS versus ECT (n=4)** HDRS Difference in Change from Baseline WMD 5.97 points (95% CI, 0.94 to 11.0, ***P*** = 0.020; I^2 = 72.2%) in favour of ECT. Pooled Risk Ratio – Response 1.72 (95% CI, 0.95 to 3.11, ***P*** = 0.072; I^2 = 60.6%), favouring ECT Pooled Risk Ratio – Remission 1.44 (95% CI, 0.64 to 3.23, ***P*** = 0.375; I^2 = 69.1%), favouring ECT **Adverse Effects** **rTMS versus Sham** *"One study reported no serious adverse event in patients, and three studies did not report on adverse events. Headache and scalp discomfort were the most frequently reported adverse events in these trials, and rates were higher in rTMS-treated than sham rTMS–treated patients. The occurrence of headache in patients who received sham treatment might in fact raise questions about the integrity of sham conditions."* P. 45 **rTMS versus ECT** Five studies reported adverse events.	*"Overall, the body of evidence showed a small short-term effect of rTMS in comparison with sham for improving depression scores. There is limited data to assess the long-term effectiveness of rTMS."* P. 50 *"Trials of high-frequency rTMS of the dorsolateral prefrontal cortex versus ECT showed significantly more improvement in depression scores with ECT treatment than with rTMS treatment, and the effect estimate was also clinically significant."* P. 50 *"The remission and response rates were also higher in patients who received ECT than in those who received rTMS."* P. 50

Main Study Findings	Authors' Conclusion
For one study, adverse event scores were described as not differing by the systematic review authors. One study found higher adverse event scores with rTMS (not tested statistically; as reported by the systematic review authors). One study reported headache in one patient with rTMS. One study reported headache in 25% of rTMS patients, but no adverse events with ECT. One study reported 15% of patients had headache and 10% had sleep disturbance with rTMS, but no adverse events with ECT.	

CI = Confidence interval; CrI = Credible interval; ECT = Electroconvulsive therapy; HDRS = Hamilton Depression Rating Scale; MADRS= Montgomery–Åsberg Depression Rating Scale; OR = Odds Ratio; rTMS = Repetitive transcranial magnetic stimulation; WMD = Weighted mean difference.

[A] One study could not be included in the analysis due to the manner in which outcome data were presented.

[B] Concomitant medication was used in all but one study.

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Kaster, 2018[18]	
Remission rTMS (40.0%; 95% CI, 21.1% to 61.3%) Sham rTMS (14.8%; 95% CI, 4.2% to 33.7%, p < 0.05) **Response** rTMS (44.0%; 95% CI, 24.5% to 63.5%) Sham rTMS (18.5%; 95% CI, 3.9% to 33.2%, p < 0.05) **Baseline-Week 4 Active vs. Sham (no p-values reported)** SSI: 0.4 (95% CI, -2.2 to 2.9) SF-36: 0.9 (95% CI, -5.7 to 3.8) BSI: 1.4 (95% CI, -1.2 to 3.9) **Safety** No serious adverse events were observed. Pain was the only adverse effect more common in the active condition (16.0% vs. 0%).	*"This randomized controlled trial provides evidence for the efficacy and tolerability of high-dose deep rTMS for LLD. The H1 coil was well tolerated with only one participant dropping out due to inability to tolerate the stimulus, and pain was the only adverse effect more common with active rTMS. Based on these results, future studies with longer follow-up periods are justified to determine the role of deep rTMS for the treatment of LLD."* P. 10
Taylor, 2018[19]	
Remission (Based on MADRS) rTMS (25.0%) Sham rTMS (31%; p=0.69) **Response (Based on MADRS)** rTMS (44.0%) Sham rTMS (31%; ***P*** = 0.46)	"*In conclusion, we have conducted a randomized, controlled study of rTMS in moderately depressed patients and demonstrated that symptom improvement was associated with decreasing connectivity of the sgACC within the AN and with DMN and FP networks."* P. 12

Main Study Findings	Authors' Conclusion
No statistically significant differences on other endpoints including HRSD-17, QIDS-SR, GAD-7, WSAS, and GAF (relevant data not shown).	
Valkonen-Korhonen, 2018[20]	
Full remission (**Based on HDRS Score)** rTMS (n=4) Sham rTMS (n=6) *P* = 0.47 **Treatment response** (**Based on HDRS Score)** rTMS (n=8) Sham rTMS (n=11) *P* = 0.32	*"When assessing the effect of any new stimulation treatment, the tendency for spontaneous recovery from depression should be considered. However, it is especially important to investigate the role of unspecific effects of the stimulation treatments, such as rehabilitative activation and social support provided by the rTMS treatment setting. These and placebo effects should be better acknowledged in order to better understand the effects of brain stimulation per se."* P. 591
Yesavage, 2018[21]	
Remission Rate (HDRS) Odds ratio: 1.16 (95% CI, 0.59 to 2.26; *P* = 0.67) **Difference between rTMS and Sham in change from baseline to end of acute treatment in depression symptoms severity, mean (SD)** HDRS score: 1.28 (95% CI, −1.42 to 3.97; *P* = 0.34) MADRS score: 2.26 (95% CI, −0.91 to 5.44; *P* = 0.16) BDI score: 2.22 (95% CI, −0.64 to 5.08; *P* = 0.12) **Difference between rTMS and Sham in change from baseline to end of acute treatment in suicidal ideation, mean (SD)** BSI score: 0.08 (95% CI, −1.46 to 1.62; *P* = 0.91) **Difference between rTMS and Sham in change from baseline to end of acute treatment in PTSD symptom severity, mean (SD)** CAPS score: 5.20 (95% CI, −0.49 to 10.89; *P* = 0.07) PCL-M score: 2.68 (95% CI, −0.84 to 6.19; *P* = 0.13) **Difference between rTMS and Sham in change from baseline to end of acute treatment in quality of life, mean (SD)** VR-36 standardized PCS: −1.32 (95% CI, −3.61 to 0.97; *P* = 0.27) VR-36 standardized MCS: −1.76 (95% CI, −5.91 to 2.39; *P* = 0.40) **Adverse events** The most common nonserious adverse events included nasopharyngitis (8 participants in both groups), depression (8 active and 3 sham participants), and falls (3 active and 7 sham participants). Headache, an adverse event commonly associated with rTMS, occurred in 15 active and 16 sham participants.	*"This study supports the clinical observation that a combination of interventions including rTMS is effective for achieving symptom remission in 39.0% of veterans with MDD who were previously treatment resistant."* P. 891

Main Study Findings	Authors' Conclusion
Kang, 2016[22]	
Treatment response (**Based on HDRS Score)** rTMS (n=9/12) Sham rTMS (n=0) *P* <0.001 **Treatment remission** (**Based on HDRS Score)** rTMS (n=3/12) Sham rTMS (n=0) *P* =0.229	*"High frequency rTMS over the lDLPFC had therapeutic effects in patients with treatment-resistant major depression."* P. e1142

AN = Affective network; BDI = Beck Depression Inventory; BSI = Beck Scale for Suicide Ideation; CAPS = Clinician-Administered PTSD Scale; CI =Confidence Interval; DMN = default mode network; FP = Frontal parietal; GAD-A = Generalized Anxiety Disorder Assessment; GAF = Global Assessment of Function; HDRS = Hamilton Depression Rating Scale; lDLPFC = Left dorsolateral prefrontal cortex; LLD=Late life depression; MADRS = Montgomery–Åsberg Depression Rating Scale; MDD = Major depressive disorder; PTSD = Post-traumatic stress disorder; PCL-M = Post-Traumatic Stress Disorder Checklist Military Version; QIDS = Quick Inventory of Depressive Symptoms; rTMS = Repetitive transcranial magnetic stimulation; SD=Standard deviation; sgACC = subgenual anterior cingulate cortex; ; SF-36 = 36-Item Short Form Survey; SSI = Scale for Suicidal Ideation; VR-36 standardized PCS=Veteran's RAND-36 Physical Component Summary; VR-36 standardized MCS = Veteran's RAND-36 Mental Component Summary; WSAS = Work and Social Adjustment Scale.

Table 12: Summary of Findings of Included Economic Evaluations

Main Study Findings	Authors' Conclusion
Zhao, 2018[23]	
Inpatient **ICER per QALY gained with ECT versus rTMS** SGD 311,024 **Incremental Cost per Remission achieved with ECT versus rTMS** SGD 143,811 *Outpatient* **ICER per QALY gained with ECT versus rTMS** SGD 78,819 **Incremental Cost per Remission achieved with ECT vs. rTMS** SGD 36,444 **Probabilistic Sensitivity Analysis** *"Cost-effectiveness findings were sensitive to changes in relative risk for remission between rTMS and ECT and cost for hospitalization due to ECT"* P. 380 *"Based on probabilistic sensitivity analysis, at WTP threshold of SGD 70,000, rTMS was highly likely to be cost-effective compared to ECT"* P. 380	*"In conclusion, our study demonstrated that rTMS was a cost-effective treatment compared to ECT in TRD over one year. The cost-effectiveness of rTMS was attenuated when compared to ECT in outpatient setting. Our findings served to inform clinical decision making by considering treatment effects, cost, and patient characteristics. Studies with long-term follow-up and larger populations are warranted to further ensure the robustness of findings on the comparative effectiveness between rTMS and ECT."* P. 381

Main Study Findings	Authors' Conclusion
Health Quality Ontario, 2016[25]	
rTMS compared with ECT *Base Case Economic Model* **ICER per QALY gained with ECT compared with rTMS** C$37,640.66 *One-Way Sensitivity Analysis* *"The sensitivity analyses revealed that these results are quite robust across a range of parameters for all comparisons. The results were most sensitive to the rate of ECT, the rate of rTMS, and the cost of rTMS."* P. 23 *Probabilistic Sensitivity Analysis* *"Given a willingness to pay of $50,000 per QALY, there is a 45%* *chance that rTMS would be cost-effective. Given a willingness to pay of $100,000 per QALY, there is a 20% chance that rTMS would be cost-effective."* P. 23 **rTMS compared with sham** *Base Case* **ICER per QALY gained with rTMS compared with sham (added to pharmacotherapy)** C$98,242.37 *Probabilistic Sensitivity Analysis* *"If willingness to pay is $50,000 per QALY, there is only 2% chance that rTMS would be more cost-effective than sham rTMS. However, if the willingness to pay increases to $100,000 per QALY, the probability* *that rTMS would become more cost-effective than sham rTMS rises to 45%."* P. 23	*"Relative to repetitive transcranial magnetic stimulation, electroconvulsive therapy would be cost-effective if the willingness to pay is greater than $37,640 per quality-adjusted life-year (QALY). In comparison to pharmacotherapy, rTMS would be cost-effective when the willingness to pay is greater than $98,242 per QALY."* P. 36
Vallejo-Torres, 2015[24]	
ICER per QALY gained - ECT versus rTMS *Base Case Economic Model* ECT alone dominates with either utility estimate used in the model. *Deterministic Sensitivity Analysis* **"***We found that applying 50% upper and lower limits around each of the resource-use figures reported in the UK study did not impact on our results. The parameters that we found to have some impact on the results were the ECT and rTMS treatment costs, for which we found that in the case of acute rTMS treatment costs was 50% lower (or ECT costs 50% higher) while holding the remaining parameters constant, then the incremental cost per QALY gained of ECT alone compared to rTMS would be around €40000."* P. 1468	*"This evaluation shows that ECT is likely to be the most cost-effective option for the treatment of resistant severe depression given the estimated lower effectiveness of rTMS and the lack of evidence regarding cost savings related to the use of rTMS."* P. 1468

CND = Canadian; ECT = Electroconvulsive therapy; ICER = Incremental cost-effectiveness ratio; QALY = Quality adjusted life year; rTMS = Repetitive transcranial magnetic stimulation; SGD = Singapore dollars; TRD = Treatment resistant depression.

Table 13: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
CANMAT, 2016[26]	
rTMS is considered a first line treatment for patients who have failed at least one antidepressant	Level 1 evidence for efficacy, level 3 evidence for safety, no strength of recommendation
rTMS protocols *First line* High-frequency rTMS to left DLPFC Low-frequency rTMS to right DLPFC	Level 1 evidence; no strength of recommendation
Second line Bilateral rTMS to DLPFC (left high-frequency and right low-frequency)	Level 1 evidence, no strength of recommendation
Low-frequency rTMS to right DLPFC (in nonresponders to high-frequency left DLPFC-rTMS) or high-frequency rTMS to left DLPFC (in nonresponders to low-frequency right DLPFC-rTMS)	Level 3 evidence, no strength of recommendation
Third line High-frequency rTMS to bilateral DMPFC	Level 3 evidence, no strength of recommendation
Veterans Affairs/Department of Defense, 2016[27]	
"We suggest offering treatment with repetitive transcranial magnetic stimulation (rTMS) for treatment during a major depressive episode in patients with treatment-resistant MDD." P. 49	"Weak for" (i.e., in favour of"); No level of evidence provided

DLPFC = Dorsolateral prefrontal cortex; DMPFC = Dorsomedial prefrontal cortex; MDD = Major depressive disorder; rTMS = Repetitive transcranial magnetic stimulation.

Appendix 5: Overlap between Included Systematic Reviews

Table 14: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation		
	Sehatzadeh 2019[15]	Papadimitropoulou 2017[16]	Health Quality Ontario, 2016[17]
Theleritis 2017[12]	X		
Blumberger 2016[11]	X		
Chen 2013[30]	X	X	X
Bakim 2012[31]	X	X	X
Blumberger 2012[32]	X	X	X
Fitzgerald 2012[33]	X	X	X
Keshtkar 2011[34]			X
Zhang 2011[35]		X	X
George 2010[36]	X	X	X
Pallanti 2010[37]	X	X	
Triggs 2010[38]	X	X	X
Fitzgerald 2009[39]		X	
Bretlau 2008[40]	X		X
Mogg 2008[41]	X		X
Eranti 2007[42]			X
Loo 2007[43]			X
O'Reardon 2007[44]	X		X
Stern 2007[45]			X
Avery 2006[46]	X		X
Fitzgerald 2006[47]	X		
Garcia-Toro 2006[48]	X	X	
McDonald 2006[49]	X		
Rosa 2006[50]			X
Rossini 2005[51]		X	
Su 2005[52]	X		X
Holtzheimer 2004[53]	X		X
Mosimann 2004[54]	X		X
Fitzgerald 2003[55]			X
Grunhaus 2003[56]			X
Hoppner 2003[57]			X

Primary Study Citation	Systematic Review Citation		
	Sehatzadeh 2019[15]	Papadimitropoulou 2017[16]	Health Quality Ontario, 2016[17]
Boutros 2002[58]	X		X
Padberg 2002[59]			X
Garcia-Toro 2001[60]	X		X
Berman 2000[61]	X		X
Grunhaus 2000[62]			X
Pridmore 2000[63]			X
Avery 1999[64]	X		X
Loo 1999[65]			X