TITLE: Transcranial Magnetic Stimulation for the Treatment of Adults with PTSD, GAD, or Depression: A Review of Clinical Effectiveness and Guidelines

DATE: 31 October 2014

CONTEXT AND POLICY ISSUES

Post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), and depression are psychiatric disorders that interfere with daily-life activities.[1-3] In Canada, the prevalence of PTSD is approximately 12%, 2.6% for GAD and 8% for depression.[4-6] These mental disorders result from brain dysregulation, such as neurological over-arousal (e.g. anxiety), neurological under-arousal (e.g. depression) or instable-arousal (e.g. PTSD), in that patients have problems in intentionally controlling neural functioning.[7] Patients with mental health disorders usually require pharmacological and/or psychological interventions such as cognitive-behavioral therapy,[8] however approximately two-thirds of patients with major depressive disorder do not have adequate responses to conventional treatments.[8]

A potential alternative to pharmacological and psychological interventions are brain stimulation techniques such as transcranial magnetic stimulation (TMS). TMS is a non-invasive technique,[9] whereby a small coil placed over a patient's scalp. The electric current circulating through the coil produces a magnetic field which can then pass through the scalp and bone and induce changes in nerve cell activity in the cortex.[10-13] The effect of the magnetic stimulation is dependent on location, intensity and frequency of the magnetic pulses.[9] Its repetitive form is referred to as repetitive TMS (rTMS), and has been used for diagnostic and therapeutic purposes in a variety of neuropsychiatric disorders.[9,14] Two emergent forms of TMS include theta-burst magnetic stimulation (TBS) and EEG-based synchronized TMS (sTMS). TBS involves the use of a triple-pulse burst in either a continuous or intermittent form and is thought to induce longer-lasting effects, while it is the intent of sTMS to identify the most optimal stimulation protocol for an individual patient in real-time.

TMS was initially used to investigate nerve conduction.[13] It can be used as a tool for brain mapping, as a probe for neuronal networks, and as a modulator of brain function.[15] Clinically, brain stimulation has been found to improve symptoms of depression,[13] however due to the multifactorial nature of the intervention, the overall effectiveness of TMS for the treatment of

depression remains unclear. Even less well known is the efficacy and effectiveness of TMS for the treatment of PTSD and GAD.

The purpose of this report is to review the clinical effectiveness of TMS for treating PTSD, GAD and depression, and to summarize the guidelines that are associated with the use of TMS for these conditions.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of transcranial magnetic stimulation for the treatment of adults with posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), or depression?

2. What are the guidelines associated with the use of transcranial magnetic stimulation for the treatment of adults with posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), or depression?

KEY FINDINGS

There is early evidence in the form of two systematic reviews and one RCT that TMS may offer improved clinical outcomes for patients with PTSD. There were no primary research studies found in the systematic review assessing the use of rTMS for treating patients with GAD. Four HTAs indicate that while evidence tends to demonstrate the effectiveness of rTMS, it is insufficient to draw conclusions regarding the use of TMS for treating patients with depression; additional systematic reviews and meta-analyses for the use of TMS for treating depression have also reported benefits. Five guideline documents include recommendations regarding the use of TMS in practice, but are variable between organizations.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 9), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2004 and September 30, 2014.

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	Adults with post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), or depression
Intervention	Transcranial magnetic stimulation
Comparator	No active treatment Standard therapy
Outcomes	Clinical effectiveness and benefit Guidelines
Study Designs	Health technology assessment (HTA), systematic review, meta-analysis, randomized controlled trials (RCTs), evidence-based guidelines

Exclusion Criteria

Primary research articles were excluded if they were cited in a corresponding systematic review, meta-analysis or health technology assessment. Systematic reviews were excluded if they were cited in a review of systematic reviews or health technology assessment reports. All RCTs conducted within the search date range cited by the most recent systematic review were excluded.

Critical Appraisal of Individual Studies

The assessment of the quality of the included HTAs was guided by the checklist developed by the International Network of Agencies for Health Technology Assessment (INAHTA).[16] Meta-analyses and systematic reviews were assessed using AMSTAR.[17] RCTs were assessed using the Downs and Black checklist.[18] Evidence-based guidelines were assessed using the AGREE tool.[19] Numerical scores were not calculated. Instead, the strengths and limitations of individual studies were summarized and presented.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 465 citations. Five additional studies were identified by searching the grey literature. After screening titles and abstracts, 121 potentially relevant studies were selected for full-text review. Among these 121 studies, 92 were excluded because they did not meet the selection criteria. Appendix 1 describes the PRISMA flowchart of the included studies in the report.

Twenty-nine studies were included in in the review: one meta-analysis, one systematic review and one RCT related to TMS for PTSD; one systematic review related to TMS for GAD; four HTAs, two systematic reviews of meta-analyses, nine systematic reviews, and five RCTs related to TMS for depression; and five evidence-based guidelines.

Summary of Study Characteristics

A detailed summary of included studies is provided in Appendix 2.

Clinical Effectiveness of TMS for Adults with PTSD

One meta-analysis[20] and one systematic review[21] were identified in the literature search, both originating from the United States. The objective of the meta-analysis was to identify all RCTs assessing the use of TMS compared to sham-TMS for the treatment of PTSD published up until July 2013.[20] The systematic review was broader in scope, searching more databases, including RCTs, non-RCTs, crossover trials and observational studies, and assessing the efficacy of all complementary and alternative medicine interventions for the treatment of PTSD, including rTMS, published up until March 2013.[21] Both reviews identified three relevant RCTs.

One RCT[22] was identified subsequent to the searches of the included systematic reviews. The RCT originated from Korea and assessed the efficacy and tolerability of rTMS compared to sham-rTMS in treating PTSD based on changes in Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS) scores from baseline to a 2, 4, and 8 week follow-up.

Clinical Effectiveness of TMS for Adults with GAD

One systematic review[23] was identified in the literature search, originating from Germany. The objective of this study was to provide an overview of the effects of rTMS on anxiety in animals and humans. No search criteria (i.e. databases accessed, key words used, search dates, types of studies, etc.) were specified, and there were no primary research studies identified assessing the effectiveness of TMS for GAD.

Clinical Effectiveness of TMS for Adults with Depression

Four HTAs were conducted between 2004 and 2014; two from Canada[24,25] and two from the United States.[2,26] The three most recent publications[2,24,26] assessed the efficacy of rTMS in individuals with treatment-resistant depression. Sham-rTMS was one of the comparators of interest in all reports. Other comparators included conventional therapy, electroconvulsive therapy (ECT), and variations in rTMS stimulation parameters. Outcomes were based on response or remission rates and adverse effects.

Two systematic reviews of meta-analyses were conducted.[12,27] The Canadian study[27] identified 11 meta-analyses indexed in PubMed and published between January 2000 and October 2011, and the Italian study[12] identified 15 meta-analyses or systematic reviews in PubMed published between January 1980 to December 2010. Both reviews aimed to assess the efficacy of rTMS for the treatment of major depression. The Italian review[12] focused on individuals with treatment-resistant depression. Both reviews compared rTMS to sham-rTMS and did not specify their outcomes of interest.

Nine systematic reviews of primary studies, seven of which included meta-analyses, were conducted. The reviews originated from the United Kingdom,[28] Germany,[29] India,[30] Canada,[31] The Netherlands,[32] the United States,[33] Australia,[34] and two from China.[35,36] The terminology for the type of depression varied across studies but was classified as one or more of the following: depression,[28,30] acute depression,[33] major depression,[29,31,32,34-36] or treatment-resistant depression.[28] All studies assessed the use of rTMS compared to sham-rTMS, ECT, or conventional therapy. Brunoni et al.[33] assessed the use of rTMS in combination with antidepressants. Outcomes included the percentage change in depression scores on one or multiple scales including the Hamilton Depression Rating Scale (HDRS), Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), or the number of

remissions or responders. Remission or response is often defined as a 50% or more reduction in baseline outcome measure score (i.e. HDRS, MADRS, BDI) at follow-up.
Five RCTs were conducted since the search cut-off date of the most recent systematic review. The studies originated from France,[37] Israel,[38] Germany,[39] Taiwan,[40] and the United States.[41] Compared to previous studies which assessed conventional rTMS vs. sham-rTMS, these recent studies compared the efficacy of one sub-form of rTMS versus sham-rTMS or in combination with antidepressant medication. Three studies assessed the use of theta-burst stimulation (TBS) (both continuous and intermittent forms),[38-40] one study was a pilot to assess EEG-based synchronized TMS (sTMS),[41] and one study combined active-rTMS with the antidepressant venlafaxine.[37] All studies assessed the use of the intervention for treating major depression and assessed similar outcomes as the systematic reviews.

Evidence-Based Guidelines Associated with the use of Transcranial Magnetic Stimulation for Adults with PTSD, GAD or Depression

Five evidence-based guidelines were identified in the literature search. One guideline originated from the Canadian Network for Mood and Anxiety Treatments (CANMAT) in Canada,[42] two from the United States (American Psychiatric Association, APA and the Department of Veterans Affairs and The Department of Defense, VA/DoD),[43,44] one from a group of European experts[45] and one from the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom.[46] The European guideline focused on the use of TMS for treating a range of disorders including PTSD and depression,[45] while the others contained recommendations for the use of TMS in managing or treating PTSD, depression, or major depression.[42-44,46] Variable methods were used across guideline documents for the grading of recommendations. Appendix 2, Table A2.3 outlines the criteria used in each.

Summary of Critical Appraisal

A detailed description of individual study critical appraisal is provided in Appendix 3.

Clinical Effectiveness of TMS for Adults with PTSD

Both systematic reviews had very broad search criteria, identifying studies that used TMS for treating PTSD.[20,21] Wahbeh et al.[21] was more explicit in describing their inclusion criteria, process of study selection and method of quality assessment compared to Karsen et al[20] (i.e. the data extraction process was described a priori and study screening and extraction were done by two independent reviewers). Karsen and colleagues[20] did not detail any inclusion/exclusion criteria, their process of study selection, or test for publication bias. Publication bias was mentioned as a possible limitation by Wahbeh et al.,[21] due to the inclusion of 17 positive trials and five negative trials, however it was not explicitly tested. The methods used in the meta-analysis[20] are also concerning because two studies contributed two sets of data to the pooled effect size. This may have led to an inflation of results due to the overrepresentation of two of the three studies.

The RCT[22] ensured blinding of patients and assessors, provided a detailed description of the intervention, but did have some limitations. The time frame of recruitment and method of allocation were not described, study power was a concern, and the results may not be generalizable to all patients with PTSD. The traumatic events experienced by patients included in this study were non-military in nature, including patients having experienced a motor vehicle accident, domestic violence or physical assaults.

Clinical Effectiveness of TMS for Adults with GAD

The review conducted by Zwanger et al.[23] described itself as a systematic review; however it did not follow the protocol of a properly conducted systematic review. Inclusion and exclusion criteria were not listed; there was no detail of the search strategy, study selection and data extraction process, and had no reported assessment of study quality. The definition of anxiety, which included PTSD and panic disorder, was unclear and not what is typically seen in the literature.

Clinical Effectiveness of TMS for Adults with Depression

The quality of the 2014 Canadian HTA report[24] was high. The scope and context of the report are well described; the methods for searching the literature, extracting data, and critically appraising the studies are well documented and conducted. Multiple databases were accessed, screening and study selection were done in duplicate, and standardized forms were used to extract study data. Furthermore, an economic analysis was completed, and the social implications and implementation concerns were discussed. The HTAs from the United States[2,26] were also well conducted but variable. The Agency for Healthcare Research and Quality accessed multiple literature databases and study screening and selection was done by two independent reviewers, whereas the Blue Cross and Blue Shield Association only searched PubMed and did not report having completed study screening in duplicate. The scope of the report was also limited in that an economic analysis was not completed and patient and family perspectives were not considered in drawing conclusions regarding the use of TMS for treating depression in adults.

The two identified systematic reviews of meta-analyses[12,27] provided a list of included studies, the characteristics of each, and a qualitative review of their findings. The comprehensiveness of the search was limited because only PubMed was accessed, and it is unclear if the study screening, selection and data extraction were done in duplicate. Finally, the reviews discussed the quality of the individual studies, however it was unclear if the level of quality was appropriately considered when the authors stated their conclusions.

The included systematic reviews[33,34] and meta-analyses[28-32,35,36] were generally of high quality. The objectives of the study and the literature search strategy were all presented a priori. In more recent reviews,[28-30,35,36] the study selection and data extraction was done in duplicate and reasons for the exclusion of specific studies were provided. In most studies, where it was applicable, study heterogeneity and publication biases were assessed,[29-32,35,36] as was the quality of included studies.[30,31,35] Heterogeneity between studies was found in some cases.[30,31] The small sample sizes of the studies included in two reviews[30,36] were highlighted as limitations to the cited benefits of rTMS. The subgroup analysis performed by Xie et al.[36] (according to stimulation parameters frequency, number of stimuli, motor threshold and treatment duration) may be of concern given the limited sample size included for each parameter. Finally, the generalizability of findings by Sarkar et al.[30] may be limited due to its focus on studies published in the Indian context.

The included RCTs[37-41] were generally of high quality based on the reporting by study authors. All authors stated that blinding and randomization took place, however the authors of one study mentioned the inherent limitations of using sham coils in TMS[38] and details of the methods of randomization were not stated in two studies.[38,40] The objectives, interventions, patient characteristics, and outcome measures in all studies were well described. In some cases, the

underlying population from which the sample was recruited from was not well defined,[37,40,41] specific *P*-values were not reported,[38] methods of allocation were unclear,[40,41] and drop-out rate was a concern.[39] Where drop-out rate was a concern in one study,[39] the authors accounted for missing values using the last observation carried forward method.

Guidelines Associated with the use of Transcranial Magnetic Stimulation for Adults with PTSD, GAD or Depression

All evidence-based guideline documents were based on a systematic search of the literature. A clear link between the evidence and recommendations was provided in some documents,[42,45] but was less explicit in others.[43,44,46] Generally, all guidelines provided recommendations that were easily identifiable in their respective documents.[42-46] Most guidelines appropriately described the competing interests of their working group members, but there was no discussion of how these conflicts were, if at all, addressed. The level of specificity and ambiguity of the guidelines varied across guidelines, with Canadian guidelines[42] offering a reasonable synopsis of where rTMS fits into therapy for depression and recommendations for specific rTMS stimulation parameters. The American guidelines[43,44] generally had less specific recommendations while the European guidelines[45] offered a similar level of specificity as the Canadian guidelines.[42] The European guidelines[45] were unique in that they provided a discussion of the resource implications for implementing TMS into practice.

Summary of Findings

A detailed summary of individual study findings is provided in Appendix 4.

Clinical Effectiveness of TMS for Adults with PTSD

The pooled results of the meta-analysis[20] found a statistically significant improvement in PTSD symptoms for TMS compared to sham-TMS. Similar findings were cited in the systematic review[21] with Grade 'A' evidence for rTMS in treating PTSD. However, the generalizability of these findings is difficult due to the broad patient inclusion criteria, the heterogeneity between studies, and small sample sizes.

A single RCT[22] reported the effectiveness of TMS versus sham-TMS in improving PTSD symptoms. There were statistically significant differences in improvements for the active compared to the sham rTMS group for the total score and the re-experiencing domain of the CAPS. There were no between group differences in improvements between the two groups for the avoidance and hyperarousal domains of the CAPS. The authors suggest that the improvement in PTSD symptom scores for the sham-rTMS group may have been the result of natural disease improvement, the placebo effect, as well as concomitant use of antidepressants.

Clinical Effectiveness of TMS for Adults with GAD

The systematic review[23] identified in the literature search reported no studies assessing the use of rTMS for treating patients with GAD.

Clinical Effectiveness of TMS for Adults with Depression

Although the evidence in the HTAs tended to demonstrate the effectiveness of rTMS, all HTAs were unable to provide strong conclusions regarding the effectiveness of TMS for treating adults

with depression due to lack of consistent evidence,[26] the weak literature base,[24] and the methodological concerns of the existing studies.[25]

Both systematic reviews of meta-analyses stated that there is evidence to indicate that rTMS is effective compared to sham-rTMS.[12,27] There was also consensus that the reported effectiveness is dependent on the outcome measures used,[27] the characteristics of the patients,[27] and the stimulation parameters implemented.[12,32,36] Dell'osso et al.[12] stated that recent studies support low frequency rTMS, but the long-term benefits are uncertain.

In the systematic reviews of primary studies, compared to sham-rTMS, active rTMS showed moderate effects,[29] but the therapeutic effect and clinical meaningfulness of the these results have been questioned.[28] rTMS was cited as being a reasonable option,[31] but compared to ECT, all reviews have found higher levels of responses and remissions in the ECT group.[28,31,35,36] Due to the heterogeneity of stimulation parameters and comparator groups between studies, the generalizability and interpretability of these findings are difficult.

The most recent RCTs[37-41] assessing the effectiveness of rTMS for treating depression have found mixed results. There was no difference in outcomes between active and sham-cTBS,[38] however, the intermittent and intermittent plus continuous form of TBS both showed improvements in outcomes relative to sham TBS in another study.[40] Plewnia et al.[39] found improvements in MADRS scores with active-TBS, but not in HDRS or BDI. There is also preliminary data to show that sTMS offered improvements in depression scores relative to sham-sTMS.[41] Finally, combination therapy of venlafaxine and rTMS did not offer any added benefit compared to rTMS or venlafazine therapy alone.[37] The ability to draw conclusions on the alternate forms of rTMS and the combination rTMS/antidepressant medication is difficult due to the limited availability of evidence.

Evidence-Based Guidelines Associated with the use of Transcranial Magnetic Stimulation for Adults with PTSD, GAD or Depression

Evidence-based guidelines for the use of TMS in the treatment of PTSD are mixed. VA/DoD recommendations[44] from the United States state that there is insufficient evidence for the use of TMS as a first-line therapy, but that it may be considered as an alternative treatment in specific cases (i.e. patients who are treatment resistant, or have a severe and chronic condition). European guidelines[45] indicate that there is Level C evidence for the use of high frequency, right sided stimulation for the treatment of PTSD.

No Evidence-based guidelines exist for the use of TMS in the treatment of GAD.

Evidence-based guidelines for the use of TMS for the treatment of depression are also mixed. NICE guidelines[46] state that TMS should be used only for research purposes, while Canadian guidelines recommend it as a second-line treatment[42] or as an option for patients with unipolar but not bipolar depression, and under specific stimulation parameters.[45] The United States APA guidelines[43,44] offer some flexibility in their recommendations stating that an initial treatment modality for depression could include pharmacotherapy, psychotherapy, or other therapies such as rTMS, depending on a patient's clinical features and preferences.

Limitations

The evidence for the use of TMS for treating adults with PTSD is still in its early stages. A meta-analysis was conducted to overcome the limitations of having few studies and small sample sizes; however the resulting heterogeneity between studies and populations becomes a concern for the validity and generalizability of findings.

No primary research studies have assessed the use of TMS for GAD.

Numerous well-conducted HTAs, systematic reviews and meta-analyses have been completed to assess the use of TMS in the treatment of depression. These reports consistently identify that the strength of the evidence is low due to poorly conducted RCTs and due to the variability in the characteristics of the population, outcome measures used, and TMS stimulation parameters. There is some evidence for the effectiveness of TMS, however, the ideal stimulation parameters are unknown, and studies assessing its effectiveness against conventional treatments are limited.

More research is needed in order to make evidence-based recommendations for the use of TMS in treating GAD. There are evidence-based guidelines for the use of TMS in treating PTSD and depression however the depth of the guidelines is variable. Some guidelines are more specific, indicating the stimulation parameters that should be used, while others only make a statement regarding its placement in therapy (i.e. first, second or third-line therapy).

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Conventional pharmacological non-pharmacological treatments for PTSD, GAD and depression may not be sufficient for some patients. TMS is an alternative therapy that could be used in these patients, often classified as “treatment resistant”. Relative to sham-treatment, TMS has shown positive effects, for both conventional forms of TMS as well as its sub-forms such as TBS and EEG-guided sTMS. However, due to the methodological limitations of the primary research studies, health technology assessments have been unable to provide concrete conclusions and policy decisions regarding its use in practice. The evidence is strongest for the use of TMS in treating depression, but is more limited for PTSD, and very limited for GAD. While much of the literature indicates ECT is comparatively more effective than TMS, further research involving the use of TMS compared to other alternative or conventional therapies for PTSD and depression may help clarify its position in therapy. Further complicating decision making for TMS are the variations in stimulation parameters that can be used for treatment (i.e. number of pulses, frequency of pulses, number of sessions, etc.) and the characteristics of the patients that are involved in treatment. Assessing the effects of treatment according to stimulation parameter and patient population being treated may help clarify the clinical effectiveness and help guide recommendations and policy decisions.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. The human face of mental health and mental illness in Canada [Internet]. Ottawa: Government of Canada; 2006. [cited 2014 Oct 23]. Available from: http://www.phac-aspc.gc.ca/publicat/human-humain06/pdf/human_face_e.pdf

2. Psychological treatments and pharmacological treatments for adults with post-traumatic stress disorder (PTSD) [Internet]. Rockville (MD): Agency for Healthcare Research and Quality; 2011. [cited 2014 Oct 23]. (Evidence-based practice center systematic review protocol). Available from: http://effectivehealthcare.ahrq.gov/ehc/products/347/901/PTSD-Adults_Protocol_20111220.pdf

3. Meditation programs for stress and well-being [Internet]. Rockville (MD): Agency for Healthcare Research and Quality; 2012. [cited 2014 Oct 23]. (Evidence-based practice center systematic review protocol). Available from: http://effectivehealthcare.ahrq.gov/ehc/products/375/981/MeditationProgramsForStressAndWellbeing_Protocol_20120222.pdf

4. Statistics Canada. Section B - anxiety disorders. Part 6 - post traumatic stress disorder (PTSD) [Internet]. In: Health state descriptions for Canadians. Ottawa: Statistics Canada; 2013 [cited 2014 Oct 8]. Available from: http://www.statcan.gc.ca/pub/82-619-m/2012004/sections/sectionb-eng.htm#a6.

5. Statistics Canada. Section B - anxiety disorders. Part 4 - generalized anxiety disorder [Internet]. In: Health state descriptions for Canadians. Ottawa: Statistics Canada; 2013 [cited 2014 Oct 14]. Available from: http://www.statcan.gc.ca/pub/82-619-m/2012004/sections/sectionb-eng.htm.

6. Statistics Canada. Section A - affective disorders. Part 1 - major depression [Internet]. In: Health state descriptions for Canadians. Ottawa: Statistics Canada; 2013 [cited 2014 Oct 15]. Available from: http://www.statcan.gc.ca/pub/82-619-m/2012004/sections/sectiona-eng.htm#a1.

7. Russell-Chapin LA, Chapin TJ. Neurofeedback: a third option when counseling and medication are not sufficient [Internet].Counseling Outfitters; 2011. [cited 2014 Aug 18]. Available from: http://counselingoutfitters.com/vistas/vistas11/Article_48.pdf

8. Clinical practice guidelines. Management of anxiety disorders. Can J Psychiatry [Internet]. 2006 Jul [cited 2014 Aug 18];51(8 Suppl 2):9S-91S. Available from: http://ww1.cpa-apc.org:8080/Publications/CJP/supplements/july2006/anxiety_guidelines_2006.pdf

9. Pallanti S, Bernardi S. Neurobiology of repeated transcranial magnetic stimulation in the treatment of anxiety: a critical review. Int Clin Psychopharmacol. 2009 Jul;24(4):163-73.

10. Berlim MT, Van den EF, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med. 2014 Jan;44(2):225-39.

11. Berlim MT, Van den EF, Daskalakis ZJ. A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. Psychol Med. 2013 Nov;43(11):2245-54.

12. Dell'osso B, Camuri G, Castellano F, Vecchi V, Benedetti M, Bortolussi S, et al. Meta-review of metanalytic studies with repetitive transcranial magnetic stimulation (rTMS) for the treatment of major depression. Clin Pract Epidemiol Ment Health [Internet]. 2011 [cited 2014 Oct 7];7:167-77. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3227860/pdf/CPEMH-7-167.pdf

13. Transcranial magnetic stimulation for depression. Technol Eval Cent Assess Program Exec Summ [Internet]. 2011 Jul [cited 2104 Oct 10];26(3):1-4. Available from: http://www.bcbs.com/blueresources/tec/vols/26/26_3.pdf

14. Hoppner J, Broese T, Wendler L, Berger C, Thome J. Repetitive transcranial magnetic stimulation (rTMS) for treatment of alcohol dependence. World J Biol Psychiatry. 2011 Sep;12 Suppl 1:57-62.

15. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry. 2010 Jul;71(7):873-84.

16. INAHTA Secretariat. A checklist for health technology assessment reports [Internet]. Version 3.2. Edmonton (AB): INAHTA Secretariat; 2007 Aug. [cited 2014 Oct 23]. Available from: http://www.inahta.org/wp-content/uploads/2014/04/INAHTA_HTA_Checklist_English.pdf

17. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2014 Oct 31];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

18. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2014 Oct 30];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

19. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ [Internet]. 2010 Dec [cited 2014 Apr 9];182(18):E839-E842. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/pdf/182e839.pdf

20. Karsen EF, Watts BV, Holtzheimer PE. Review of the effectiveness of transcranial magnetic stimulation for post-traumatic stress disorder. Brain Stimul. 2014 Mar;7(2):151-7.

21. Wahbeh H, Senders A, Neuendorf R, Cayton J. Complementary and alternative medicine for posttraumatic stress disorder symptoms: A systematic review. J Evid Based Complementary Altern Med. 2014 Mar 27;19(3):161-75.

22. Nam DH, Pae CU, Chae JH. Low-frequency, repetitive transcranial magnetic stimulation for the treatment of patients with posttraumatic stress disorder: a double-blind, sham-controlled study. Clin Psychopharmacol Neurosci [Internet]. 2013 Aug [cited 2014 Oct 9];11(2):96-102. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3766761/pdf/cpn-11-96.pdf

23. Zwanzger P, Fallgatter AJ, Zavorotnyy M, Padberg F. Anxiolytic effects of transcranial magnetic stimulation--an alternative treatment option in anxiety disorders? J Neural Transm. 2009 Jun;116(6):767-75.

24. Health Technology Assessment Unit, University of Calgary. Repetitive transcranial magnetic stimulation for treatment resistant depression. A health technology assessment [Internet]. Calgary (AB): University of Calgary; 2014 Aug 6. [cited 2014 Oct 17]. Available from: http://www.health.alberta.ca/documents/AHTDP-rTMS-Resistant-Depression-UofC.pdf

25. Health Quality Ontario. Repetitive transcranial magnetic stimulation for the treatment of major depressive disorder: an evidence-based analysis. Ont Health Technol Assess Ser [Internet]. 2004 [cited 2014 Oct 7];4(7):1-98. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3387754/pdf/ohtas-04-98.pdf

26. Blue Cross Blue Shield Association, Kaiser Foundation Health Plan, Southern California Permanente Medical Group. Transcranial magnetic stimulation for depression. Technol Eval Cent Assess Program Exec Summ [Internet]. 2014 Jan [cited 2014 Oct 10];28(9):1-4. Available from: http://www.bcbs.com/blueresources/tec/vols/28/28_09.pdf

27. Hovington CL, McGirr A, Lepage M, Berlim MT. Repetitive transcranial magnetic stimulation (rTMS) for treating major depression and schizophrenia: a systematic review of recent meta-analyses. Ann Med. 2013 Jun;45(4):308-21.

28. Lepping P, Schonfeldt-Lecuona C, Sambhi RS, Lanka SV, Lane S, Whittington R, et al. A systematic review of the clinical relevance of repetitive transcranial magnetic stimulation. Acta Psychiatr Scand. 2014 Apr 12.

29. Kedzior KK, Azorina V, Reitz SK. More female patients and fewer stimuli per session are associated with the short-term antidepressant properties of repetitive transcranial magnetic stimulation (rTMS): a meta-analysis of 54 sham-controlled studies published between 1997-2013. Neuropsychiatr Dis Treat [Internet]. 2014 [cited 2014 Oct 7];10:727-56. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4019615/pdf/ndt-10-727.pdf

30. Sarkar S, Grover S. A systematic review and meta-analysis of trials of treatment of depression from India. Indian J Psychiatry. 2014 Jan;56(1):29-38.

31. Berlim MT, Van den EF, Daskalakis ZJ. Efficacy and acceptability of high frequency repetitive transcranial magnetic stimulation (rTMS) versus electroconvulsive therapy (ECT) for major depression: a systematic review and meta-analysis of randomized trials. Depress Anxiety. 2013 Jul;30(7):614-23.

32. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. Psychol Med. 2009 Jan;39(1):65-75.

33. Brunoni AR, Fraguas R, Fregni F. Pharmacological and combined interventions for the acute depressive episode: focus on efficacy and tolerability. Ther Clin Risk Manag [Internet]. 2009 [cited 2014 Oct 7];5:897-910. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2781064/pdf/tcrm-5-897.pdf

34. Frazer CJ, Christensen H, Griffiths KM. Effectiveness of treatments for depression in older people. Med J Aust. 2005 Jun 20;182(12):627-32.

35. Ren J, Li H, Palaniyappan L, Liu H, Wang J, Li C, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2014 Jun 3;51:181-9.

36. Xie J, Chen J, Wei Q. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: a meta-analysis of stimulus parameter effects. Neurol Res. 2013 Dec;35(10):1084-91.

37. Brunelin J, Jalenques I, Trojak B, Attal J, Szekely D, Gay A, et al. The efficacy and safety of low frequency repetitive transcranial magnetic stimulation for treatment-resistant depression: the results from a large multicenter French RCT. Brain Stimul. 2014 Aug 7.

38. Chistyakov AV, Kreinin B, Marmor S, Kaplan B, Khatib A, Darawsheh N, et al. Preliminary assessment of the therapeutic efficacy of continuous theta-burst magnetic stimulation (cTBS) in major depression: A double-blind sham-controlled study. J Affect Disord. 2014 Sep 1;170C:225-9.

39. Plewnia C, Pasqualetti P, Grosse S, Schlipf S, Wasserka B, Zwissler B, et al. Treatment of major depression with bilateral theta burst stimulation: a randomized controlled pilot trial. J Affect Disord. 2014 Mar;156:219-23.

40. Li CT, Chen MH, Juan CH, Huang HH, Chen LF, Hsieh JC, et al. Efficacy of prefrontal theta-burst stimulation in refractory depression: a randomized sham-controlled study. Brain. 2014 Jul;137(Pt 7):2088-98.

41. Jin Y, Phillips B. A pilot study of the use of EEG-based synchronized Transcranial Magnetic Stimulation (sTMS) for treatment of Major Depression. BMC Psychiatry [Internet]. 2014 [cited 2014 Oct 7];14:13. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3904196/pdf/1471-244X-14-13.pdf

42. Kennedy SH, Milev R, Giacobbe P, Ramasubbu R, Lam RW, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. J Affect Disord. 2009 Oct;117 Suppl 1:S44-S53.

43. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder [Internet]. 3rd. Arlington (VA): The Association; 2010. [cited

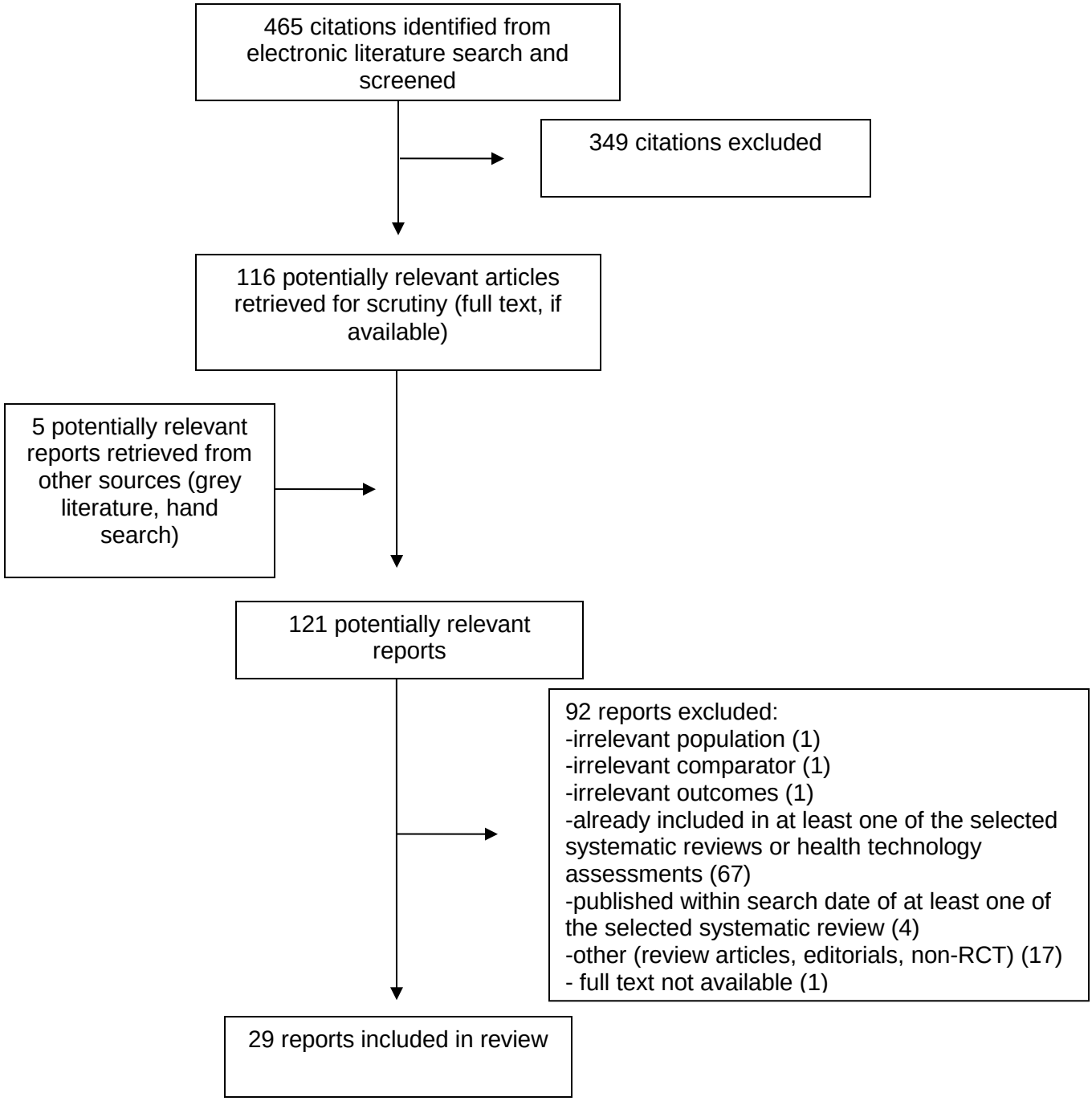
2014 Oct 17]. Available from: http://psychiatryonline.org/pdfaccess.ashx?ResourceID=243261&PDFSource=6

44. Management of post-traumatic stress. [Internet].U.S. Department of Veterans Affairs; 2010. [cited 2014 Oct 17]. Available from: http://www.healthquality.va.gov/PTSD-Full-2010c.pdf

45. Lefaucheur JP, ndre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. 2014 Jun 5.

46. National Institute for Health and Clinical Excellence. Depression in adults: the treatment and management of depression in adults [Internet]. London (UK): The Institute; 2014. [cited 2014 Oct 17]. Available from: http://www.nice.org.uk/guidance/cg90/resources/guidance-depression-in-adults-pdf

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of the Included Studies

Table A2.1: Characteristics of the Included Health Technology Assessments, Systematic Reviews and Meta-analyses

Study	Objectives	Search Parameters	Population	Intervention	Comparator	Outcomes
Post-Traumatic Stress Disorder (PTSD)						
Meta-analysis Karsen et al. 2014[20] United States	To summarize and describe the findings of studies assessing the effectiveness of rTMS to treat PTSD.	**Databases accessed:** PubMed, CINAHL, PsycINFO. **Limits:** Published up to July 2013. **Study type**: RCTs	**Inclusion criteria:** **Diagnosis**: PTSD	TMS	Sham-TMS	PTSD symptoms
Systematic Review Wahbeh et al. 2014[21] United States	To assess the efficacy of complementary and alternative medicine interventions for treating PTSD.	**Databases accessed:** MEDLINE, PsycINFO, CINAHL, Alt HealthWatch, AMED, Cochrane Library, Health Technology Assessment database. **Limits:** Variable between databases, published up to March 12, 2013. **Study type:** RCTs, non-RCTs, crossover trials, observational studies, case-control, uncontrolled pre-post (≥5)	**Inclusion criteria:** **Age:** Adults **Diagnosis:** PTSD or individuals completing a PTSD assessment.	Complementary or alternative medicine intervention as defined by the National Institutes of Health National Center for Complementary and Alternative Medicine	Not specified	PTSD symptoms
Generalized Anxiety Disorder (GAD)						
Systematic Review Zwanzger et al. 2009[23] Germany	To provide an overview of the effects of rTMS on anxiety in animals and humans.	**Limits:** Animal and human studies.	Not specified	rTMS	Not specified.	Not specified.
Depression						
Health Technology Assessment The Health	To assess the social impact, efficacy, safety and cost-effectiveness	**Databases accessed:** MEDLINE, Cochrane Library, PubMed, EMBASE, PsychINFO,	**Inclusion criteria:** **Age**: ≥ 18 years **Diagnosis**: depression (unipolar or bipolar)	rTMS	Sham-rTMS Other (ECT, pharmaceuticals etc.)	Response rates, remission rates, adverse effects.

Study	Objectives	Search Parameters	Population	Intervention	Comparator	Outcomes
Technology Assessment Unit, University of Calgary 2014[24] Canada	of rTMS compared to alternative interventions for individuals with treatment resistant depression.	HTA Database. **Limits**: Published up to January 10 2014, humans **Study type**: RCTs	**Prior treatment**: treatment-resistant (variable definitions)		Variations in rTMS parameters ECT	
Health Technology Assessment Blue Cross and Blue Shield Association 2014[26] United States	To determine the effect and adverse effects of TMS as a treatment for depression (update of 2011 review – Blue Cross Shield 2011).	**Databases accessed:** MEDLINE **Limits:** English language, human studies **Study type:** Meta-analyses (from 2010 to November 2013), Sham-controlled trials, >150 patients	**Inclusion Criteria:** **Diagnosis**: Depression **Prior treatment**: patients who had a non-response to one prior round of antidepressant therapy.	rTMS	Sham-rTMS	50% reduction in depressive symptoms (MADRS, HAMD, CGI, IDS). Adverse effects: morbidity, complications or discomfort
Health Technology Assessment Agency for Healthcare Research and Quality 2011[2] United States	To compare the efficacy, effectiveness and safety of nonpharmalogical (ECT, rTMS, VNS, or psychotherapy) interventions to pharmalogical interventions for treating treatment-resistant depression.	**Databases accessed:** MEDLINE, Embase, Cochrane, PscINFO, International Pharmaceutical Abstracts **Limits:** 1980 to November 2010, English language, human studies **Study type:** variable depending on question	**Inclusion Criteria:** **Age**: Adults **Diagnosis**: Depression **Prior treatment:** Patients who had a non-response to two prior rounds of antidepressant therapy.	rTMS	Sham-rTMS ECT	Response, remission, relapse, recurrence, health-related quality of life, satisfaction, functioning and productivity. Adverse effects: side-effects, adherence
Health Technology Assessment Medical Advisory Secretariat 2004[25] Canada	To determine the effectiveness and cost-effectiveness of rTMS for treating major depressive disorder.	**Databases accessed:** MEDLINE, EMBASE, INAHTA, DARE, Cochrane database, ACP Journal Club **Limits:** January 1996 to March 2004, English language, human studies **Study Type:** Systematic	**Inclusion criteria:** **Diagnosis:** Major depressive disorder	rTMS **Parameters:** (standalone or add-on)	Sham-rTMS ECT Conventional care	Time-related end-points (length of time depression or relapse-free, time to adjunctive treatment, time to return to work, time to hospital admission/discharge), decrease in

Study	Objectives	Search Parameters	Population	Intervention	Comparator	Outcomes
		reviews, RCTs, non-RCTs (≥20 patients), cost-effectiveness studies				depressive symptoms, change in antidepressant use. Adverse effects
Systematic Review of Meta-analyses Hovington et al. 2013[27] Canada	To provide a qualitative summary of the efficacy of rTMS for treating major depression, examine the parameters that increase efficacy and provide recommendations for the conduct of future studies.	**Databases accessed:** PubMed **Limits:** January 2000 to October 2011, English language **Study Type:** Meta-analysis	**Inclusion criteria:** **Age:** ≥18 years **Diagnosis:** Major depression or schizophrenia	rTMS	Sham-rTMS	Not Specified
Systematic Review of Meta-analyses Dell'osso et al. 2011 [12] Italy	To assess the efficacy and safety of rTMS for treating major depression and treatment resistant depression.	**Databases accessed:** PubMed **Limits:** January 1980 to December 2010, English language **Study Type:** Meta-analyses and systematic reviews	**Inclusion criteria:** **Diagnosis:** Major depression or treatment resistant depression	rTMS	Sham-rTMS	Not Specified
Meta-Analysis Kedzior et al. 2014[29] Germany	To determine the short-term effects of rTMS for treating depression, to compare the results of the updated meta-analysis to the previously published meta-analysis, and to determine if there patient or treatment properties associated with	Studies included those documented in the previous meta-analysis, and those identified in an updated literature search: **Databases accessed:** PsycInfo, Medline, Cochrane library **Limits:** January 2008 to August 2013 **Study Type:** Meta-analyses	**Inclusion criteria:** **Diagnosis:** Major depressive disorder or episode	rTMS **Parameters:** **Location:** dorsolateral prefrontal cortex (unilateral or bilateral)	Sham-rTMS	Change in depression score from baseline to end of treatment.

Study	Objectives	Search Parameters	Population	Intervention	Comparator	Outcomes
	rTMS treatment effects.					
Meta-Analysis Lepping et al. 2014[28] United Kingdom	To assess the efficacy of rTMS for treating depression and treatment-resistant depression.	**Databases accessed:** MEDLINE, Embase, PsycINFO, PubMed, Cochrane library **Limits:** Published up to January 15, 2014, English language, human studies **Study Type:** RCTs and non-RCTs	**Inclusion criteria:** **Age:** Adult **Diagnosis:** Depression	rTMS **Parameters:** (standalone or add-on)	Sham-rTMS Variations in rTMS parameters ECT	% change in HAM-D scores from baseline to the last time point recorded.
Meta-Analysis Ren et al. 2014[35] China	To compare rTMS to ECT for the treatment of depression.	**Databases accessed:** PubMed, Embase, Medline, Cochrane library, Psycinfo, Chinese databases **Limits:** Published up to November 26, 2013, English and Chinese languages **Study Type:** RCTs	**Inclusion criteria:** **Diagnosis:** Major depressive episode.	rTMS **Parameters:** **Location**: dorsolateral prefrontal cortex **Frequency**: High or low	ECT	**Primary:** response (≥50% reduction in HAM-D from baseline to end of treatment), remission (based on the HAM-D), acceptability (rate of discontinuation), mental state (HAM-D score) **Secondary**: cognitive functioning (change in scores) and mental state (BPRS and BDI)
Meta-analysis Sarkar et al. 2014[30] India	To assess the efficacy and effectiveness of antidepressants and other interventions for treating depression in India.	**Databases accessed:** PubMed, PsycInfo, Google Scholar, Peer-reviewed Indian Journals **Limits:** Published up to January 2013, English Language, Human studies **Study Type:** Controlled studies	**Inclusion criteria:** **Diagnosis**: Depression	rTMS **Parameters:** (add on to antidepressant therapy)	Sham-rTMS **Parameters:** (add on to antidepressant therapy)	HAM-D, MADRS, BPRS, SIGH-D
Meta-analysis Xie et al. 2013[36]	To determine if rTMS is an appropriate	**Databases accessed:** PubMed, CCTR, Web of Science, Embase, 2	**Inclusion criteria:** **Age**: >18 years **Outcomes**: Assessed	rTMS	ECT	**Primary**: Odds of response (50% reduction in HDRS

Study	Objectives	Search Parameters	Population	Intervention	Comparator	Outcomes
China	substitution for ECT for treating major depression and if outcomes vary depending on the rTMS parameters employed.	Chinese databases **Limits:** Published up to December 2012, English and Chinese studies **Study Type:** RCTs	with HDRS **Exclusion Criteria:** **Diagnosis**: specific type of depression, or secondary to another condition **Therapy**: starting antidepressant therapy at the same time of enrollment.			score) **Secondary**: Odds of remission (HDRS-24 score ≤11 or HDRS≤17; MADRS score ≤6), and odds of drop-out.
Meta-Analysis Berlim et al. 2013[31] Canada	To compare the effectiveness of rTMS and ECT for treating major depression.	**Databases accessed:** MEDLINE, EMBASE, PsycINFO, Cochrane Library, SCOPUS **Limits**: Published between January 1 1995 and September 22, 2012. **Study Type:** randomized trials (≥5 patients per arm)	**Inclusion criteria:** **Age**: 18-75 years **Diagnosis**: major depressive episode **Exclusion Criteria:** **Diagnosis**: specific type of depression, or secondary to another condition **Therapy**: starting antidepressant therapy at the same time of enrollment, previous receipt of HF-rTMS or ECT **Outcomes**: unavailable remission rates or depression scores	rTMS **Parameters:** **Frequency:** High **Location**: left dorsolateral prefrontal cortex **Duration**: ≥10 sessions	ECT	**Primary**: Number of remissions (HAM-D score ≤7 or ≤8; MADRS score ≤6) **Secondary**: Changes in depression scores. **Other**: treatment acceptability (number of dropouts)

Study	Objectives	Search Parameters	Population	Intervention	Comparator	Outcomes
Meta-analysis Schutter 2009[32] The Netherlands	To assess the antidepressant effects of rTMS.	**Databases accessed:** PubMed, Web of Science **Limits:** Published between January 1980 and November 2007, English Language. **Study Type:** RCTs	**Inclusion criteria:** **Age:** Adults **Diagnosis**: Major depressive episode, no psychosis.	rTMS **Parameters:** **Frequency**: High (>5Hz) **Intensity**: >80% motor threshold **Location**: left dorsolateral prefrontal cortex **Duration**: ≥5 sessions	Sham-rTMS	% change in HAM-D or MADRS scores from baseline
Systematic Review Brunoni et al. 2009[33] United States	To assess the use of neurostimulation treatments in combination with antidepressants to treat the acute episode of depression.	**Databases accessed:** MEDLINE, Web of Science, Cochrane library, Scielo. **Limits:** Published between May 2004 and May 2009, English language **Study Type:** Clinical trials	**Inclusion criteria:** **Diagnosis:** acute depression	Neurostimulation therapies (rTMS, ECT, tDCS) + antidepressants	Sham-neurostimulation therapies (rTMS, ECT, tDCS) + antidepressants	Remission (HAM-D < 8), response (50% reduction in depressive symptoms)
Systematic Review Frazer et al. 2005[34] Australia	To summarize the evidence for the effectiveness of treatments for depression in people over 60 years.	**Databases accessed:** PubMed, PsycInfo, Cochrane library **Limits**: Published up to November 30, 2004 **Study Type:** Meta-analyses, RCTs, other studies if necessary.	**Inclusion criteria:** **Age:** ≥60 years **Diagnosis:** Major depression or a high level of depressive symptoms.	TMS	Not specified	Effectiveness of the intervention was graded using the National Health and Medical Research Council levels of evidence.

RCT = Randomized Controlled Trial; rTMS = repetitive Transcranial Magnetic Stimulation; PTSD = Post-Traumatic Stress Disorder; ECT = Electroconvulsive Therapy; BPRS = Brief Psychiatric Rating Scale; BDI = Beck Depression Inventory; SIGH-D = Structured Interview Guide for the Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; CCTR = Cochrane Central Register of Controlled Trials; HDRS = Hamilton Depression Rating Scale; HAM-D = Hamilton Depression Rating Scale; DARE = Database of Abstracts of Reviews of Effects; INAHTA = International Network of Agencies for Health Technology Assessment; HTA = Health Technology Assessment; AMED = The Allied and Complementary Medicine Database

Table A2.2: Characteristics of the Included Randomized Controlled Trials

Study	Objectives	Population	Intervention, Comparator	Outcomes
Post-Traumatic Stress Disorder (PTSD)				
Randomized Controlled Trial Nam et al. 2013[22] Korea	To assess the efficacy and tolerability of rTMS for treating PTSD.	N = 16 (89% were randomized and completed the study) **Population Characteristics:** **Mean age:** Intervention group 36.3±8.8 years; Comparator group 32.8±6.9 years **Sex**: Intervention group 43% male; Comparator group 33% male **Diagnosis**: DSM diagnosed PTSD **Type of traumatic events**: non-military (motor vehicle accidents, domestic violence, physical assaults) **Time since event:** mean time 3.3 years	**Active rTMS:** - **Frequency**: 1-Hz rTMS - **Total number of pulses**: 18,000 (100% RMT) - **Duration of treatment:** 20 minutes/day for 15 days (weekdays only) - **Location**: Right prefrontal cortex **Sham-rTMS** - Same protocol as intervention group, with an alternate placement of the coil. Note: Existing treatment strategies (pharmacological and non-pharmacological) continued during the trial.	**Primary:** Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS) (re-experiencing, avoidance, hyperarousal and total scores) **Assessment time points:** Baseline, 2, 4, and 8 weeks.
Depression				
Randomized Controlled Trial Brunelin et al. 2014[37] France	To assess the effect of rTMS as a standalone therapy or a combined therapy in patients with treatment resistant depression.	N = 155 (91% were randomized and completed the study) **Inclusion criteria:** DSM diagnosed major depressive disorder **Exclusion criteria**: <18 years, previous receipt of rTMS, presence of rTMS contraindications, failure to respond to venlafaxine during the current episode. **Population Characteristics:** **Mean age:** rTMS Group 53.3±11.3 years; Venlafaxine Group 56.2±9.9 years; rTMS + Venlafaxine Group 54.2±11.9 years. **Sex**: rTMS Group 37% male; Venlafaxine Group 31% male; rTMS + Venlafaxine Group 32% male. **Duration of Diagnosis:** rTMS	All patients progressed through an initial wash-out phase followed by a 2-6 week treatment period. Patients were randomized to one of three groups: **1. Active rTMS + placebo venlafaxine** - Frequency: 1-Hz rTMS - Total number of pulses: 120% RMT - Duration of treatment: 6 trains, 1 min each (with 30 seconds break in between) during weekdays only for 2-6 weeks. - Location: Right prefrontal cortex **2. Sham-rTMS + active venlafaxine** - Active venlafaxine started at 75mg for 3 days, then 150mg for 4 weeks with the option to increase to 225mg for the last 2 weeks. - Sham-rTMS involved the delivery of sham stimulations to the ipsilateral supraorbital area. **3. Combined active rTMS and venlafaxine** - As described above	**Primary:** Remission (i.e. HDRS score <8) **Secondary**: HDRS scores (continuous), MADRS scores, response (50% reduction in scores from baseline) **Other**: global clinical status, anxiety Adverse events. **Assessment time-points**: Baseline and end of treatment (6 weeks)

Study	Objectives	Population	Intervention, Comparator	Outcomes
		Group 16.2±11.7 years; Venlafaxine Group 20.5±11.2 years; rTMS + Venlafaxine Group 17.3±12.1 years.		
Randomized Controlled Trial Christyakov et al. 2014[38] Israel	To assess the efficacy of continuous theta-burst stimulation (cTBS) for the treatment of major depression.	N=29 (patients hospitalized due to clinical condition) **Exclusion criteria:** other disorders (seizure, brain damage due to head trauma in past year), risks (suicide) or contraindications to TMS (e.g. pacemaker or metallic implants). **Population Characteristics (total sample):** **Mean age:** 51.8±14.2 years **Sex**: 34% male **Duration of Diagnosis:** 14.9±11.9 years.	Patients were randomized to either active or sham cTBS: 1. **Active cTBS** - Frequency: 5-Hz rTMS (200ms between each burst, triple-pulse 50Hz bursts) - Total number of pulses: 3600 stimuli per session (4 trains of 900 stimuli, 15 min interval between each), 100% of active motor threshold. - Duration of treatment: Given for 10 weekdays. - Location: Right prefrontal cortex (in position to simulate the contralateral abductor pollicis brevis muscle) 2. **Sham cTBS** - Similar parameters as above using a sham coil	**Primary**: >50% reduction in HDRS **Assessment time-points:** weekly
Randomized Controlled Trial Plewnia et al. 2014[39] Germany	To assess the effect of a combination of intermittent excitatory (left-side) and continuous inhibitory (right-side) TBS for the treatment of depression.	N = 32 (patients hospitalized due to clinical condition) **Inclusion criteria:** right handed, 18-75 years, diagnosis of major depression. **Exclusion criteria:** other disorders (seizure, brain injuries, substance abuse), risks (pregnancy) or contraindications to TMS (e.g. pacemaker or metallic implants). **Population Characteristics (total sample):** Concurrent medication: all patients were on antidepressant medication prior to and during the trial.	Patients were randomized to receive either active or sham TBS: 1. **Active TBS** - Intermittent TBS over the left prefrontal cortex (2 seconds every 10 seconds, 20 times) - Continuous TBS over the right prefrontal cortex (40 seconds) - Total number of pulses: 200ms between each burst, triple-pulse 50Hz bursts (80% of total motor threshold) - Duration: Given for 30 weekdays. 2. **Sham TBS** - Both hemispheres	**Primary**: >50% reduction in MADRS **Secondary**: HDRS, BDI. **Assessment time points:** weekly
Randomized Controlled Trial	To assess the comparative efficacy	N = 60	Patients were randomized to one of four treatment groups. Patients received two weeks of treatment on weekdays	**Primary**: % change in HDRS (Responders

Study	Objectives	Population	Intervention, Comparator	Outcomes
Li et al. 2014[40] Taiwan	of intermittent and continuous TBS and a combination of both for the treatment of major depression. The study also aimed to assess the efficacy of TBS according to the patient's type of refractoriness.	**Inclusion criteria**: 21-70 years, diagnosis of major depression, >2 antidepressant treatments. **Exclusion criteria:** History of conditions such as psychotic disorders, bipolar disorder, substance abuse, personality disorders, neurological disorders, or had any contraindication of TMS (e.g. metallic implants or pacemakers). **Population Characteristics:** **Age**: Mean ranged from 42.4 years in Group B to 49.2 years in Group A. **Sex**: Ranged from 47% male in Group B to 27% female in Groups C and D.	only (10 sessions). All TBS was provided at triple-pulse 50Hz bursts at a frequency of 5Hz with 200ms in between, 80% of active motor threshold. 1. Group A **(continuous TBS):** Total number of pulses: 18000 (120 second continuous stimulation consisting of 1800 pulses). Location: right DPFC. 2. Group B **(intermittent TBS):** total number of pulses: 18000 (2 second stimulations repeated every 10 seconds for 570 seconds). Location: left DPFC. 3. Group C **(intermittent and continuous TBS)** 4. **Sham TBS**: Equivalent number of sessions, different coil position.	defined as those with ≥50% reduction in score) **Other**: Safety **Assessment time points**: weekly
Randomized Controlled Trial Jin et al. 2014[41] United States	A pilot study to assess the efficacy of sTMS for the treatment of depression.	N=52 **Inclusion criteria**: >18 years, diagnosis of major depression, stable medication regimen at least 1 month prior to enrollment. **Exclusion criteria**: pregnancy, diagnosed with another psychiatric condition, significant comorbidities such as thyroid disorders, history of substance abuse. **Population Characteristics**: **Age**: Active group 42.5 (15.0) years; sham group 46.3 (12.7) years **Sex**: Active 45% male; sham 44% male **Duration of Depression**: Active group 11.1 months (9.7); sham group 13.6 months (11.4).	Patients were randomized to one of three groups. Patients received a 30 minute session five days per week for four weeks. 1. **Fixed frequency magnet rotation using sTMS** (according to the patients individual apha frequency) 2. **Random frequency magnet rotation using sTMS** 3. **Sham treatment using sTMS** with non-magnetized steel cylinders.	**Primary**: % reduction in HDRS scores. **Secondary**: Safety **Assessment time points:** weekly

RCT = Randomized Controlled Trial; rTMS = repetitive Transcranial Magnetic Stimulation; PTSD = Post-Traumatic Stress Disorder; DSM = Diagnostic and Statistical Manual; RMT = Resting Motor Threshold; CAPS = Clinician-Administered Posttraumatic Stress Disorder; HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; cTBS = continuous Theta-Burst Stimulation; BDI = Beck Depression Inventory; DPFC = Dorsolateral Prefrontal Cortex; NICE = National Institute for Health and Clinical Excellence

Table A2.3: Characteristics of the Included Evidence-Based Guidelines

Guideline Document, Origin, Year	Objectives, Population	Grading of Recommendations
Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) Lefaucheur et al. 2014[45] Europe	To provide guidelines for the use of rTMS in the treatment of various conditions and disorders. Conditions include depression, anxiety disorders, and others (e.g. pain, tinnitus and schizophrenia etc.)	All studies were first assigned a Study Class: (pg. 7) Class I: "adequately data-supported, prospective, randomized, placebo- controlled clinical trial with masked outcome assessment in a representative population (n≥25 patients receiving active treatment). It should include (a) randomization concealment; (b) clearly defined primary outcomes; (c) clearly defined exclusion/inclusion criteria; (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias, and (e) relevant baseline characteristics substantially equivalent among treatment groups or appropriate statistical adjustment for differences. Class II: randomized, placebo-controlled trial performed with a smaller sample size (n < 25) or that lacks at least one of the above-listed criteria a–e. Class III: all other controlled trials. Class IV: uncontrolled studies, case series, and case reports." Each recommendation was then assigned a Level: (pg.7) Level A:"("definitely effective or Ineffective") requires at least 2 convincing Class I studies or one convincing Class I study and at least 2 consistent, convincing Class II studies." Level B: "("probably effective or ineffective") requires at least 2 convincing Class II studies or one convincing Class II study and at least 2 consistent, convincing Class III studies." Level C: "("possibly effective or ineffective") requires one convincing Class II study or at least 2 convincing Class III studies."
Management of Post-Traumatic Stress Department of Veterans Affairs (VA) and The Department of Defense (DoD) United States 2010[44]	To update the VA/DoD guideline document from 2010. Adult patients with PTSD who are treated at a VA or DoD clinical facility.	Levels of Evidence: (pg. 201) I: At least one properly done RCT II-1: Well-designed controlled trial without randomization II-2: Well-designed cohort or case-control analytic study, preferably from more than one source II-3: Multiple time series evidence with/without intervention, dramatic results of uncontrolled experiment III: Opinion of respected authorities, descriptive studies, case reports, and expert committees Quality of Evidence: (pg. 201) Good: High grade evidence (I or II-1) directly linked to health outcome Fair: High grade evidence (I or II-1) linked to intermediate outcome; *or* Moderate grade evidence (II-2 or II-3) directly linked to health outcome Poor: Level III evidence or no linkage of evidence to health outcome

Guideline Document, Origin, Year	Objectives, Population	Grading of Recommendations
		Overall Evidence Rating System (pg. 201-202) A: A **strong** recommendation that clinicians provide the intervention to eligible patients. *Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.* B: A recommendation that clinicians provide (the service) to eligible patients. *At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.* C: No recommendation for or against the routine provision of the intervention is made. Intervention may be **considered**. *At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.* D: A Recommendation **against** routinely providing the intervention to asymptomatic patients. *At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.* I: **Insufficient** evidence to recommend for or against routinely providing the intervention. *Evidence that the intervention is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*
Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies Canadian Network for Mood and Anxiety Treatments (CANMAT) Canada 2010[42]	To update the CANMAT guideline document from 2001. Adult patients with Major Depressive Disorder.	Interventions were first assigned a level of evidence. Level of Evidence: (pg. S45) Level 1: At least 2 RCTs with adequate sample sizes, preferably placebo controlled, and/or meta-analysis with narrow confidence intervals. Level 2: At least 1 RCT with adequate sample size and/or meta-analysis with wide confidence intervals Level 3: Non-randomized, controlled prospective studies or case series or high quality retrospective studies Level 4: Expert opinion/consensus Each intervention was then placed in a treatment hierarchy. Line of Treatment: (pg. S45) First-line: Level 1 or Level 2 evidence, plus clinical support Second-line: Level 3 evidence or higher, plus clinical support Third-line Level 4 evidence or higher, plus clinical support
Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition	To update the APA guideline document from 2000. Adult patients with Major Depressive Disorder.	Coding system for each recommendation: [I]: Recommended with substantial clinical confidence [II]: Recommended with moderate clinical confidence [III]: May be recommended on the basis of individual circumstances

Guideline Document, Origin, Year	Objectives, Population	Grading of Recommendations
American Psychiatric Association (APA) Practice Guidelines United States 2010[43]		
Depression in adults. The treatment and management of depression in adults. National Institute for Health and Clinical Excellence (NICE) United Kingdom 2009[46]	To provide a partial update and replacement to NICE Guideline CG23 (Depression: management of depression in primary and secondary care) published in 2004 and revised in 2007. Adult patients with depression.	No grading criteria stated for recommendations.

rTMS = repetitive Transcranial Magnetic Stimulation; VA/DoD = Veterans Affairs/Department of Defense; PTSD = Post-Traumatic Stress Disorder; RCT = Randomized Controlled Trial; CANMAT = Canadian Network for Mood and Anxiety Treatments; APA = American Psychiatric Association

APPENDIX 3: Critical Appraisal of the Included Studies

Table A3.1: Critical Appraisal of the Included Health Technology Assessments, Systematic Reviews and Meta-analyses

Study	Strengths	Limitations
Post-Traumatic Stress Disorder (PTSD)		
Karsen et al. 2014[20] United States	- Databases accessed, key search terms and publication date range was described a priori - Reference lists of included trials were reviewed for additional studies. - Authors of included studies were contacted for missing data. - Characteristics of included studies were provided.	- Limits such as language, publication type or publication status was not described. - No description of inclusion/exclusion criteria for the individual trials (i.e. adults, medical diagnosis of PTSD etc.) - List of excluded studies and reasons for exclusion was not included. - Process of study selection was not described. Unknown if done in duplicate by two reviewers. - No reported assessment of study quality. - Heterogeneity cited, but not tested. - Publication bias not assessed. - For trials where more than one effect size was reported (i.e. results for rTMS using high and low frequency or right vs. left localization), multiple effect sizes from a single study were included as separate entries in the meta-analysis.
Wahbeh et al. 2014[21] United States	- Study objectives, databases accessed, key search terms, publication date range and data extraction procedures were described a priori. - Screening and data extraction completed in duplicate. - Characteristics of included studies were included. - Study quality was assessed using quality assessment tools. - Reasons for study exclusion were provided. - Conflicts of interest and funding sources were described.	- Publication bias was discussed, but not assessed. - A list of excluded studies was not provided.
Generalized Anxiety Disorder (GAD)		
Zwanger et al. 2009[23] Germany	- Objective of study stated. - Results of individual studies were summarized.	- Databases accessed, key search terms and publication date range were not described. - Limits such as language, publication type or publication status was not described. - No description of inclusion/exclusion criteria for the individual trials (i.e. medical diagnosis of anxiety etc.) - List of excluded studies and reasons for exclusion was not included. - Process of study selection was not described. Unknown if done in duplicate. - No reported assessment of study quality.

Study	Strengths	Limitations
Depression		
Health Technology Assessment The Health Technology Assessment Unit, University of Calgary 2014[24] Canada	- No conflicts of interests were declared by authors. - Policy question, research question, and the scope of the report are stated. - Literature search strategy is provided (databases, year range, inclusion/exclusion criteria). - Standardized extraction forms used. - Patient/family perspectives are considered. - Critical appraisal and synthesis of data was well described and completed. - Economic analysis was provided. - Social implications and implementation concerns were considered.	- A list of excluded studies is not provided. - Unclear if other information resources such as the grey literature were searched. - Unclear if report was reviewed externally.
Health Technology Assessment Blue Cross and Blue Shield Association 2014[26] United States	- No conflicts of interests were declared by authors. - Literature search strategy is provided (databases, year range, inclusion/exclusion criteria). - Statement of objective was included. - Study quality was assessed.	- Limited databases were search (only searched Medline via. Pubmed) - Unclear if report was reviewed externally - Economic analysis was not provided. - Social implications and implementation concerns were not discussed.
Health Technology Assessment Agency for Healthcare Research and Quality 2011[2] United States	- Research questions and scope of the report are stated. - Conflicts of interest were declared and addressed. - Literature search strategy is provided (databases, year range, inclusion/exclusion criteria). - Screening, selection and quality scoring completed by two independent reviewers - Study quality was assessed. - Reasons for exclusions reported - Report was reviewed by external stakeholders. - Sources of information in addition to the peer reviewed literature were included.	- Economic analysis was not provided. - No evidence of a discussion of ethical, legal and social implications of the technology. - Patient/family perspectives were not sought.
Health Technology Assessment Medical Advisory Secretariat 2004[25] Canada	- Research questions and scope of the report are stated. - Policy implications, including social concerns are discussed. - Literature search strategy is provided (databases, year range, inclusion/exclusion criteria). - Economic analysis was provided.	- No statement regarding conflicts of interest. - Do not state details of the population of interest beyond Major Depressive Disorder. - No mention if study selection and extraction were completed in duplicate. - Excluded studies are not listed and reasons for their exclusion are not provided.

Study	Strengths	Limitations
Systematic Review of Meta-analyses Hovington et al. 2013[27] Canada	- Research question was stated a priori. - Inclusion/exclusion criteria stated. - Reference lists of the included studies were reviewed. - The characteristics of the included studies were provided. - Conflict of interest statement was included.	- Only PubMed was searched in the review. - Unclear if the study screen, selection and extraction were done in duplicate. - No a priori specification of comparator or outcomes.
Systematic Review of Meta-analyses Dell'osso et al. 2011 [12] Italy	- Research question was stated a priori. - A list of included studies and their characteristics was provided. - The quality of included studies was discussed qualitatively. - Conflict of interest statement was included.	- Only PubMed was searched in the review. - Unclear if the study screen, selection and extraction were done in duplicate. - No a priori specification of outcomes.
Meta-Analysis Kedzior et al. 2014[29] Germany	- Research question was stated a priori. - Inclusion/exclusion criteria stated. - Comprehensive search of the literature. - Data extracted by two independent reviewers. - The characteristics of the included studies were documented. - Performed analysis for publication bias. - Conflict of interest statement was included.	- A list of excluded studies was not provided. - The quality of the study was assessed statistically but not pragmatically.
Meta-Analysis Lepping et al. 2014[28] United Kingdom	- Research question was stated a priori. - Inclusion/exclusion criteria stated. - Comprehensive search of the literature. - Data extracted by two independent reviewers. - The characteristics of the included studies were documented. - Conflict of interest statement was included.	- Reporting of results is unclear (no confidence intervals are reported for statistical tests.) - No forest plots provided. - No analysis of publication bias.
Meta-Analysis Ren et al. 2014[35] China	- Research question was stated a priori. - Comprehensive search of the literature. - Data extracted by two independent reviewers. - The characteristics of the included studies were documented. - Study quality was assessed. - Study heterogeneity was assessed. - Performed analysis for publication bias.	- Conflict of interest statement was not included.
Meta-analysis Sarkar et al. 2014[30] India	- Research question was stated a priori. - Comprehensive search of the literature. - Data extracted by two independent reviewers. - A list of excluded studies was reported. - Study heterogeneity was assessed. - Included studies were assessed for risk of bias. - Conflict of interest statement was included.	- Limited generalizability (only included studies originating from India).

Study	Strengths	Limitations
Meta-analysis Xie et al. 2013[36] China	- Research question was stated a priori. - Comprehensive search of the literature. - Data extracted by two independent reviewers. - Authors attempted to obtain additional information when not cited in published articles. - The characteristics of the included studies were documented. - Study heterogeneity was assessed. - Performed analysis for publication bias. - Conflict of interest statement was included.	- No list of excluded studies. - Some subgroup analysis according to stimulation parameter had limited data available.
Meta-Analysis Berlim et al. 2013[31] Canada	- Research question was stated a priori. - Comprehensive search of the literature. - Study quality was assessed as part of the inclusion criteria. - Study heterogeneity was assessed. - Publication bias was assessed - MCID for NNT reported a priori. - Conflict of interest statement was included.	- No mention if study selection and extraction were completed in duplicate. - There were differences in the baseline characteristics of the study groups. - Excluded studies are not listed and reasons for their exclusion are not provided.
Meta-analysis Schutter 2009[32] The Netherlands	- Research question was stated a priori. - Comprehensive search of the literature. - The characteristics of the included studies were documented. - Study heterogeneity was assessed. - Performed analysis for publication bias. - Conflict of interest statement was included.	- No mention if study selection and extraction were completed in duplicate. - Excluded studies are not listed and reasons for their exclusion are not provided.
Systematic Review Brunoni et al. 2009[33] United States	- Research question was stated a priori. - Comprehensive search of the literature. - The characteristics of the included studies were documented. - Conflict of interest statement was included.	- No mention if study selection and extraction were completed in duplicate. - No formal assessment of study quality.
Systematic Review Frazer et al. 2005[34] Australia	- Research question was stated a priori. - Comprehensive search of the literature.	- No mention if study selection and extraction were completed in duplicate. - Excluded studies are not listed and reasons for their exclusion are not provided. - The characteristics of the included studies were not documented in detail. - Study quality was not assessed.

PTSD = Post-Traumatic Stress Disorder; rTMS = repetitive Transcranial Magnetic Stimulation; GAD = Generalized Anxiety Disorder

Table A3.2: Critical Appraisal of the Included Randomized Controlled Trials

Study	Strengths	Limitations
Post-Traumatic Stress Disorder (PTSD)		
Nam et al. 2013[22] Korea	- Inclusion/exclusion criteria of the sample population were described. - Adverse events were reported. - Intervention is clearly described. - Patient and assessor were blind to treatment allocation.	- Time frame and details of recruitment not reported. - No description of methods for allocation. - No collection or adjustment for confounding variables. - Insufficient sample size to detect change (45% power to detect an effect size of 0.8 at a significance level of 0.05).
Depression		
Randomized Controlled Trial Brunelin et al. 2014[37] France	- Clear reporting of all relevant information (i.e. objectives, outcomes, patient characteristics etc.) - Patients were randomized into intervention groups. - Patients and assessors were blinded to intervention group. - Valid and reliable outcome measures were used. - Analysis completed according to intention to treat. - Power calculation was reported.	- The underlying population from which the sample was derived is unclear. - Last observation carried forward procedure was used for missing follow-up outcome. - No assessment of patient compliance with medication.
Randomized Controlled Trial Christyakov et al. 2014[38] Israel	- Clear reporting of all relevant information (i.e. objectives, outcomes, patient characteristics etc.) - Underlying population stated - Valid and reliable outcome measures were used. - Random allocation and blinding.	- Did not report absolute p-values (stated as $p<0.05$). - Power calculation not stated a priori; study not powered to detect statistically significant differences between groups. - Blinding was stated by authors to be compromised. - Results of all statistical tests are not reported.
Randomized Controlled Trial Plewnia et al. 2014[39] Germany	- Objectives, characteristics of patients, and intervention well described. - Study was double blind; confirmed the integrity of blinding by asking patients to state what group they were in. - Patients were randomized - Intention to treat analysis	- 20/32 patients completed the trial - Not all outcomes reported in text.
Randomized Controlled Trial Li et al. 2014[40] Taiwan	- Objectives, characteristics of patients, and intervention well described - Study was double blind; tested blinding with patients - Patients were randomized	- Starting recruitment population not well defined. - Methods of allocation unclear.
Randomized Controlled Trial Jin et al. 2014[41] United States	- Objectives, characteristics of patients, and intervention well described - Study was double blind - Patients were randomized - Discuss the possible confounding effects of the concurrent medication. - Valid and reliable outcome measures were used.	- Starting recruitment population not well defined. - Methods of allocation unclear. - Results of two different stimulation patterns were pooled.

Table A3.3: Critical Appraisal of the Included Evidence-Based Guidelines

Study	Strengths	Limitations
Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) Lefaucheur et al. 2014[45] Europe	- Overall objective, health question, target users and applicable patient population were well described. - Systematic search of the literature was undertaken. - Quality of evidence was considered in the formulation of recommendations. - Recommendations are unambiguous and easily identifiable. - Options for management are considered where applicable. - Methodological and resource implications are considered and discussed.	- Unclear if the guideline development group included representatives from all relevant processional groups and if views from patient and public groups were sought. - Criteria for study selection were unclear. - Unclear if the recommendations underwent external review prior to publication. - Process for future updates was not specified - Safety data discussed, but unclear if it was considered in providing recommendations. - Relevant completing interests of guideline development group members are stated but not addressed.
Management of Post-Traumatic Stress Department of Veterans Affairs (VA) and The Department of Defense (DoD) United States 2010[44]	- Overall objective, clinical question, target users and applicable patient population were well described. - Input from of a wide range of professional groups was sought. - Search criteria and selection criteria of the relevant literature were well described. - The quality of evidence was assessed when making recommendations - The methods for formulating the recommendations were clearly described. - There is a clear link between the recommendations and supporting evidence. - Recommendations are relatively specific.	- Unclear if guideline document was reviewed by external experts prior to publication. - Unclear if patient or public input was sought. - Process for future updates not specified. - Relevant competing interests of guideline development group members are not disclosed.
Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies Canadian Network for Mood and Anxiety Treatments (CANMAT) Canada 2010[42]	- Overall objective, clinical question and target users were described. - A systematic search of the literature was conducted and study inclusion/exclusion criteria were described. - The health benefits and harms were taken into consideration when making recommendations. - Recommendations underwent external review prior to publication. - Other options for management of depression are well described. - Recommendations are specific and easily identifiable. - There is a clear link between the recommendations and supporting evidence.	- Unclear if the guideline development group includes individuals from all relevant professional groups. - Process for future updates not specified. - Relevant conflicts of interest for the guideline development group are stated but not addressed.

Study	Strengths	Limitations
Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition American Psychiatric Association (APA) Practice Guidelines United States 2010[43]	- Overall objective, clinical question, target users and applicable patient population were well described. - Systematic search of the literature was performed. - Guidelines were reviewed by individuals from a wide range of professional groups prior to publication. - Options for therapeutic management were presented. - Implementation guidelines were presented - Competing interests of guideline development group members were reported.	- Unclear if all relevant professional groups were represented in the development of the recommendations. - Unclear if the views and preferences of the target population were sought. - Selection of evidence was not well described. - Timing and frequency of updates were not well described. - Unclear if quality of the evidence and the benefits and harms were considered in formulating the recommendations. - Recommendations for the use of TMS are ambiguous. - Competing interests of guideline development group members were not addressed.
Depression in adults. The treatment and management of depression in adults. National Institute for Health and Clinical Excellence (NICE) United Kingdom 2009[46]	- Objectives of the review and the clinical questions were well described. - Stakeholder contributions are described. - Systematic review of the literature, and clear methods for selecting relevant evidence. - Quality assessment of literature undertaken. - External review process and procedure for evidence updates were reported.	- Methods for the development of the recommendations were difficult to locate. - The link between the evidence and recommendations was unclear. - A description of the process for formulating the recommendations was difficult to locate.

rTMS = repetitive Transcranial Magnetic Stimulation; VA/DoD = Veterans Affairs/Department of Defense; CANMAT = Canadian Network for Mood and Anxiety Treatments; APA = American Psychiatric Association

APPENDIX 4: Summary of Results of the Included Studies

Table A4.1: Summary of Results of the Included Health Technology Assessments, Systematic Reviews and Meta-analyses

Study Type/ Author/Country	Key Findings	Author Conclusions
Post-Traumatic Stress Disorder (PTSD)		
Meta-analysis Karsen et al. 2014[20] United States	8 studies 3 studies (5 effect sizes – low/high frequency TMS, right/left simulation) were included in a meta-analysis. **TMS vs. TMS-sham** PTSD symptom scales, Effect size 2.67 (95% CI 1.11 to 4.23)	Authors cited that the "…effect size is most likely falsely elevated" (pg.156) due to the heterogeneity between studies, the small sample sizes, and recording outcomes immediately after treatment. The results suggest that TMS may be effective, but these are early results and further research is needed.
Systematic Review Wahbeh et al. 2014[21] United States	5 studies - 3 RCTs (high quality) - 1 pre-post - 1 crossover rTMS was cited as having Grade A, or strong scientific evidence of benefit. This Grade was given because at least 2 properly designed and conducted RCTs exist.	"Several complementary and alternative medicine modalities may be helpful for improving posttraumatic stress disorder symptoms. Repetitive transcranial magnetic stimulation has the strongest evidence for benefit." (pg. 172)
Generalized Anxiety Disorder (GAD)		
Systematic Review Zwanzger et al. 2009[23] Germany	No studies were identified to assess the impact of rTMS for treating generalized anxiety disorder. The review classifies PTSD as an anxiety disorder, for which 4 studies were identified.	"Current evidence of anxiolytic effects of rTMS in preclinical model and pilot patients or studies is still inconsistent. However, because of its non-invasive nature, rTMS is a promising experimental intervention to further investigate the function of the PFC and other cortex regions in relation to the amygdala." (pg. 772)
Depression		
Health Technology Assessment The Health Technology Assessment Unit, University of Calgary 2014[24] Canada	70 studies **rTMS vs. sham-rTMS** Response: 31 trials, RR 2.35, 95% CI 1.70 to 3.25 Remission: 18 trials, RR 2.24, 95% CI 1.53 to 3.27 Side effects: headaches and pain/discomfort in both active and sham groups. **HF-rTMS vs. LF-rTMS** Response: 11 trials, RR 1.19, 95% CI 0.97 to 1.46 Remission: 6 trials, RR 1.29, 95% CI 0.75 to 2.22 Side effects: headaches, dizziness, pain/discomfort in both groups. **Unilateral rTMS vs. Bilateral rTMS** Response: 5 trials, RR 1.15, 95% CI 0.85 to 1.56 Remission: 3 trials, RR 1.18, 95% CI 0.71 to 1.96 Side effects: headaches, agitation, pain/discomfort in both groups.	"rTMS is an effective treatment when compared to sham. Patients undergoing rTMS are twice as likely to achieve either clinical response or remission compared to patients undergoing a sham procedure." (pg. 69) The optimal frequency, location, and intensity of rTMS is unclear. "There is a trend towards high frequency rTMS being more effective to achieve both clinical response and remission than low frequency." (pg.81) "There is a trend towards bilateral rTMS being more effective to achieve both clinical response and

Study Type/ Author/Country	Key Findings	Author Conclusions
	High Intensity rTMS vs. Low Intensity rTMS Response: 11 trials, RR 1.15, 95% CI 0.54 to 2.41 Remission: 6 trials, RR 1.72, 95% CI 0.89 to 3.33 Side effects: headaches, tactile artifact, pain/discomfort in both groups. **rTMS vs. ECT** Response: 3 trials, RR1.09, 95% CI 0.79 to 1.48 Remission: 3 trials, RR 0.97, 95% CI 0.65 to 1.45 Side effects: headaches and pain/discomfort in both groups.	remission than bilateral." (pg. 88) "There is a trend towards high intensity rTMS being more effective to achieve both clinical response and remission than low intensity." (pg. 94) "The effectiveness of rTMS compared to ECT is unclear. There is a trend towards rTMS being more effective to achieve clinical response but less effective to achieve remission." (pg. 113) "The literature on this topic is weak. The included studies suggest that rTMS may be an effective intervention for treatment resistant youth and young adults; however, the evidence is too weak to be able to draw conclusions." (pg. 137)
Health Technology Assessment Blue Cross and Blue Shield Association 2014[26] United States	7 meta-analyses (Slotema et al. 2010; Allan et al. 2011; Gaynes et al. 2011; Berlim et al. 2012, 2013, 2013a, 2013b): - A total of 57 trials were included - Only 1 meta-analysis (Gaynes et al. 2011) satisfied all AMSTAR criteria. - Short-term (possibly long-term) TMS is superior to sham TMS for patients who do not respond to medication. - Publication bias and sample size was a concern. 3 RCTs with short-term results (O'Reardon et al. 2007; George et al. 2010; Unpublished RCT) - Trial quality was fair to poor. 2 RCTs with long-term results (Avery et al. 2008; McDonald et al. 2011) - Extension studies of O'Reardon et al. 2007 and George et al. 2010. - No internal control and no blinding. Adverse events reported in the literature by at least one patient: suicidal ideation, worsening depression, tension-type headaches, neck pain, neuropsychological disturbances, changes in auditory thresholds, electroencephalographic abnormalities, drowsiness, tearfulness, mania, hypomania, seizures. 66 trials ongoing.	Technology Evaluation Criteria: 1. Technology is approved by government bodies: Yes 2. The effect of the technology on patient outcomes is available from research: Evidence not adequate enough to draw conclusions. 3. Technology improves net health outcome: Evidence not adequate to draw conclusions. 4. Technology must be equally as effective to alternatives: Evidence not adequate to draw conclusions. 5. Improvement in outcomes attainable in real-life settings. No evidence available. Short-term results: "suggest, but do not provide consistent evidence, that TMS improves remission of MDD compared with a sham procedure in patients failing 1 or more antidepressant trials." Pg. 17 "For the above reasons, transcranial magnetic stimulation therapy for depression does not meet the TEC criteria."
Health Technology Assessment Agency for	**rTMS vs. sham-rTMS (Patients with 1 or more confirmed or probable prior or antidepressant medication treatment failures):** WMD in HAM-D depressive severity (12 studies) (-4.40,	The clinical relevancy of the studies to date are limited by: the definition of treatment-resistant depression, the number of head-

Study Type/ Author/Country	Key Findings	Author Conclusions
Healthcare Research and Quality 2011[2] United States	95% CI -6.04 to -2.76) RR of response (12 studies) (2.18, 95% CI 1.47 to 3.22; NNT 6, 95% CI 4 to 10) RR of remission (7 studies) (2.37, 95% CI 1.20 to 4.69) Maintenance of remission (3 trials; insufficient evidence) Cognitive functioning (4 trials; insufficient evidence) Adverse events (1 trial; significantly more scalp pain reported in rTMS group; Low level of evidence) Withdrawals due to adverse event (7 trials; mixed results; insufficient evidence) Overall withdrawals (8 trials; mixed results; insufficient evidence) Health-related outcomes (1 trial; low frequency rTMS resulted in significant improvements; Low level of evidence) **ECT vs. rTMS (Patients with 2 or more prior antidepressant treatment failures):** Change in depressive severity (1 trial; no significant difference; Low level of evidence) Response rate (1 trial; no significant differences; Low level of evidence) Remission rate (1 trial; no significant differences; Low level of evidence) Maintenance of remission (No eligible studies) Cognitive functioning (1 trial; insufficient evidence) Adverse events (No eligible studies) Withdrawals due to adverse event (1 cohort study; no significant differences; Low level of evidence) Overall withdrawals (1 trial and 1 cohort study; greater withdrawals in the ECT group; Low level of evidence) **ECT + rTMS vs. ECT (Patients with 2 or more prior antidepressant treatment failures):** Change in depressive severity (1 trial; no significant difference; Low level of evidence) Response rate (No eligible studies) Remission rate (1 trial; no significant differences; Low level of evidence) Cognitive functioning (1 trial; insufficient evidence) Adverse events (1 trial; no significant differences; Low level of evidence) Health-related outcomes (1 trial; no significant differences; Low level of evidence)	to-head comparison trials, measurements used to capture the number of treatment failures, consistency in outcome measures, and consistency in trial protocols. The strength of the evidence for the efficacy, effectiveness and safety of non-pharmacological interventions for treatment-resistant depression is low or insufficient.
Health Technology Assessment Medical Advisory Secretariat 2004[25] Canada	1 Cochrane review, 1 health technology assessment, 1 technology scan, and 4 systematic reviews and meta-analysis were identified in the review. Two of the most recent health technology assessments in the report stated that there was no evidence in support of rTMS compared to placebo or ECT. This conclusion was based on several methodological limitations of the included studies: sample size, allocation concealment, blinding, patient heterogeneity, dropouts/withdrawals, outcome measures, the presence of a placebo effect, length of studies, and heterogeneity in rTMS protocol.	"Due to several serious methodological limitations in the studies that have examined the effectiveness of rTMS in patients with MDD, it is not possible to conclude that rTMS either is or is not effective as a treatment for MDD (in treatment-resistant depression or in nontreatment-resistant depression)." (Pg. 11)
Systematic Review of Meta-analyses Hovington et al.	11 meta-analyses assessing the effectiveness of rTMS for treating major depression were identified. - Number of RCTs in the studies ranged from 5 to 34.	"Overall, M-As in MD overwhelmingly support its efficacy, with individual ES estimations being clearly

Study Type/ Author/Country	Key Findings	Author Conclusions
2013[27] Canada	- Number of patients in the individual RCTs ranged from 91 to 1383. - Prior use of antidepressants was variable - Heterogeneity between studies - Effect sizes ranged from -1.1 to 13.3 - Majority of studies found that rTMS was more effective than sham-rTMS - two studies raised concerns about accepting the conclusion due to poor quality of the included RCTs. - Adverse events: 1 case of seizure due to rTMS. Other side effects: headaches, dizziness, scalp discomfort.	influenced by the choice of outcome measures and/or by patient characteristics (including treatment resistance).” (pg.319)
Systematic Review of Meta-analyses Dell’osso et al. 2011 [12] Italy	15 studies - Number of RCTs in the studies ranged from 3 to 40. - Number of patients in the individual RCTs ranged from 91 to 1562 - Early studies show mixed results - Subsequent years continue to show mixed results. - Most recent studies support low-frequency rTMS. - Results are influenced by treatment parameters (left vs. right sided, location, length of treatment etc.) - Uncertain if there are any long-term benefits.	“Most of the work in this field has been carried out in drug-resistant patients with positive results emerging from recent metaanalyses which analyzed studies using novel and more effective stimulation parameters (e.g., a greater number of sessions).” (pg. 9)
Meta-Analysis Kedzior et al. 2014[29] Germany	54 studies (14 from the updated search and 40 from the previous meta-analysis) N=2,242 **rTMS vs. sham-rTMS** - Mean change in depression scores from baseline to last trial: weighted effect size = -0.51 (95% CI -0.63 to -0.39) - Moderator analysis: 4 studies from the updated search removed from the analysis due to an inflation of results - Publication bias: not significant	rTMS results in a moderate change in depression scores from baseline to the end of treatment. The inflation of the results due to the four studies that were subsequently excluded was likely due to the differences in the outcome measures used and the variation in the patient inclusion criteria employed.
Meta-Analysis Lepping et al. 2014[28] United Kingdom	63 studies Length of follow-up: 5 days to 24 weeks Sample size: 5 to 155 patients Baseline depression scores: 22 to 28 (HAM-D) **rTMS vs sham-rTMS (only RCTs)** - Non-treatment resistant depression: (22 trials) (% mean change 35.63 SD 16.35 vs. 23.33 SD 16.51, T=-13.85, p<0.05, No 95% CI reported) - Treatment-resistant depression: (10 trials) (% mean change 45.21 SD 10.94 vs. 25.04 SD 17.55, T = -10.10, p<0.05, No 95% CI reported) **rTMS vs. ECT** - Higher efficacy with ECT (% reduction in HAM-D 46.36, SD 27.47 for rTMS vs. 33.7% for ECT, No statistical comparison reported).	The authors report that rTMS has a positive effect on depression scores however there is also a strong placebo effect of rTMS reported. When correlated with a CGI-I score, the clinical meaningfulness of the results are of concern. “These findings create serious doubt over the clinical relevance of the therapeutic effects of rTMS.” (pg 11)
Meta-Analysis Ren et al. 2014[35]	10 randomized trials N=425 patients **rTMS vs. ECT (high and low frequency rTMS) (7 trials)**	“ECT was more effective than rTMS for major depression, especially in short-term, particularly for patients with

Study Type/ Author/Country	Key Findings	Author Conclusions
China	Response (62/145 (43%) vs. 84/134 (63%), RR 1.52, 95% CI 1.18 to 1.95) Remission (46/143 (32%) vs. 70/132 (53%), RR 1.42, 95% CI 1.16 to 1.75) Discontinuation (21/147 (14%) vs. 17/139 (12%), RR 1.17, 95% CI 0.66 to 2.08) **rTMS vs. ECT (high frequency rTMS)(7 trials)** Continuous HAM-D score difference (MD 2.15, 95% CI -0.50 to 4.81) **rTMS vs. ECT (low frequency rTMS) (1 trial)** Continuous HAM-D score difference (MD 5.50, 95% CI 2.64 to 8.36)	psychotic depression…" (pg. 187) "…no significant between-group difference in all-cause discontinuation rates between the two treatments, suggesting comparable levels of acceptability. We found both rTMS and ECT were well tolerated with only minor side effects and no serious adverse events." (pg. 187) "…current data is unable to support the superiority of one treatment over the other when outcomes beyond one month are considered." (pg 188)
Meta-analysis Sarkar et al. 2014[30] India	**3 trials** N=104 Outcome reported after 6-10 sessions. **rTMS vs. sham-rTMS** Effect size 0.74, 95% CI 0.396 to 1.084 Evidence of heterogeneity.	"…and addition of rTMS to usual treatment may be beneficial." (pg 8) "The efficacy of rTMS as an add-on treatment in this meta-analysis was found to be significant; however, it is important to note that the sample size in most of these trials have been very small." (pg.9)
Meta-analysis Xie et al. 2013[36] China	9 RCTs N=368 N_1 (rTMS) =186 N_2 (ECT) =182 **rTMS vs. ECT** Response (8 trials): 74/151 (49%) vs. 90/142 (63%), OR 0.55, 95% CI 0.34 to 0.89. Remission (7 trials): 40/131 (31%) vs. 56/122 (46%), OR 0.49, 95% CI 0.29 to 0.85) Drop-out (4 trials): 19/102 (19%) vs. 25/101 (25%), OR 0.70, 95% CI 0.36 to 1.39.	"This review provides evidence that rTMS may be an appropriate replacement for ECT under certain rTMS parameters." (pg. 6)
Meta-Analysis Berlim et al. 2013[31] Canada	7 randomized trials N=294 patients N_1 (rTMS) =150 (48.9 years; 60% female) N_2 (ECT) =144 (51.3 years; 70.8% female) Mean number of sessions: 1. HF-rTMS: 15.2±4.1 2. ECT: 8.2±1.9 **HF-rTMS vs. ECT** Remission rate (6 trials): 33.6% vs. 52%; OR 0.46 (95% CI: 0.22-0.96) For ECT, NNT: 6 (95% CI: 3.2 to 18.9) No evidence of heterogeneity. Changes in depressive symptoms (7 trials): Hedges' g: -0.93 (95% CI: -1.61 to -0.26) Evidence of heterogeneity.	The ECT group had higher HDRS scores and a shorter duration of disease. "In summary, HF-rTMS could be seen as an attractive option for depressed patients who remain significantly disabled despite the use of antidepressants or because of their inability to tolerate medication side effects and who are unable to tolerate or refuse ECT.[64] However, considering our main findings, it is unlikely that HF-rTMS will, in its current form, replace ECT for the treatment of severely ill depressed patients." (pg. 620)

Study Type/ Author/Country	Key Findings	Author Conclusions
	Dropout rates: 9.9% vs. 12.1%; OR 0.66 (95% CI 0.29-1.5)	
Meta-analysis Schutter 2009[32] The Netherlands	30 RCTs N=1164 patients N_1 = 606 (real rTMS) N_2 = 558 (sham rTMS) **rTMS vs. sham rTMS** Effect size 0.39, 95% CI 0.25 to 0.54 No evidence of heterogeneity or publication bias. **Side effects:** headaches, dizziness, nausea scalp pain (all minor)	"The results show that fast frequency rTMS over the left DLPFC is superior to sham and may be as effective as at least a subset of commercially available antidepressant medications. In addition, TMS is a safe method and because of its few side-effects is well tolerated by patients. However, at this point caution should be exercised because the integrity of blinding and the lack of a proper control condition are considered limitations of rTMS trials. In addition, age bias, medication, suboptimal stimulation parameters, lack of biological information and followup assessments may stand in the way of exploiting the effects of rTMS." (pg. 72)
Systematic Review Brunoni et al. 2009[33] United States	13 studies 4 studies assessed rTMS as an accelerant of the antidepressant effect of the medication - 3 of the 4 studies found accelerated response - 1 study found no differences between the groups 9 studies assessed rTMS as an add-on to existing antidepressant therapy - 8 of the 9 studies found a superior response in groups receiving active therapy. - 1 study found no differences between the groups	The authors conclude that using rTMS as an add-on or augmentation strategy may be an effective option for individuals with treatment-resistant depression. More research is needed to identify what population of individuals would benefit from this strategy and if the class of antidepressant influences the effectiveness.
Systematic Review Frazer et al. 2005[34] Australia	3 RCTs **TMS** No effects noted for patients at 2 weeks. Quality of Evidence: II (i.e. at least one appropriately designed RCT exists) Side Effects noted: headache, scalp discomfort, rare cases of an epileptic occurrence.	"The bulk of the evidence for TMS shows no effect on depressive symptoms in older people." (pg. 2)

rTMS = repetitive Transcranial Magnetic Stimulation; PTSD = Post-Traumatic Stress Disorder; RCT = Randomized Controlled Trial; GAD = Generalized Anxiety Disorder; CI = Confidence Interval; RR = Risk Ratio; ECT = Electroconvulsive Therapy; AMSTAR = Assessing Methodological Quality of Systematic Reviews; MDD = Major Depressive Disorder; TEC = Technology Evaluation Criteria; HAM-D = Hamilton Depression Rating Scale; HF = High-frequency; NNT = Number Needed to Treat

Table A4.2: Summary of Results of the Included Randomized Controlled Trials

Study Type/ Author/Country	Key Findings	Author Conclusions
Post-Traumatic Stress Disorder (PTSD)		
Randomized Controlled Trial Nam et al. 2013[22] Korea	Both sham-rTMS and active rTMS groups experienced a significant improvement in CAPS scores over time: - Reexperiencing domain (F=146.0; p<0.001) - Avoidance domain (F=120.3; p<0.001) - Hyperarousal domain (F=64.73; p<0.001) - Total domain (F=387.67; p<0.001) There was a statistically significant time by treatment group effects for the re-experiencing domain and total scores: - Reexperiencing domain (F=7.47; p=0.004) - Total domain (F=6.45; p=0.008) Mild adverse effects included: headache (both groups), dizziness (both groups), and difficulty concentrating (sham group only)	Both sham and active rTMS groups experienced improvements in all CAPS categories and total score. Patients in the active rTMS group experienced greater improvements in CAPS total scores and re-experiencing domain scores between baseline and follow-up time points. The authors highlight the possibility of natural improvement in depression scores, the placebo effect, and concomitant medication use as influencing the results of the trial.
Depression		
Randomized Controlled Trial Brunelin et al. 2014[37] France	No significant difference between groups for the % of patients with remission at the end of treatment (P=0.59): **Active rTMS + sham venlafazine:** 41% **Sham-rTMS vs. active venlafazine:** 43% **Active rTMS and active venlafazine**: 28% No significant difference between groups for the HDRS, MADRS or BDI outcomes: F=0.36; P=0.97, F=0.47; P=0.93, F=0.52; P=0.90 respectively. No significant difference between groups for the % of patients with remission at the end of treatment (P=1): **Active rTMS + sham venlafazine:** 59% **Sham-rTMS vs. active venlafazine:** 60% **Active rTMS and active venlafazine**: 54% No significant difference safety outcomes between the three groups or the drop-out rate.	"…the combination of LF rTMS and venlafaxine is not more efficient than venlafaxine only and rTMS only." (pg 5-6) "LF rTMS appears to be as efficient as venlafaxine and as the combination of venlafaxine and rTMS in the treatment of TRD." (pg. 6)
Randomized Controlled Trial Christyakov et al. 2014[38] Israel	There were statistically significant improvements in HDRS scores over time (F=42.4; p<0.00001) for both the active and sham TBS groups, with no differences in the degree of change over time between the groups (F=1.4; p>0.05). % of patients with ≥50% reduction in HDRS: **Active cTBS:** 33.3% **Sham cTBS:** 30.8% **Effect size (reduction in HDRS) (n=28):** At 2 weeks: 0.44 (-0.5 to 1.47)	"In conclusion, the results of this study suggest that an antidepressant effect of cTBS to the right DLPFC is, at the best, modest and does not seem to exceed that of conventional low frequency rTMS to the right DLPFC or high frequency rTMS to the left DLPFC. However, given the safety, tolerability and convenience of application of cTBS and the limitations of the present study, its potential clinical utility should not be dismissed at this point and a direct comparison between cTBS and standard TMS

Study Type/ Author/Country	Key Findings	Author Conclusions
		protocols in studies with a larger sample size is warranted." (pg. 229)
Randomized Controlled Trial Plewnia et al. 2014[39] Germany	**% Responders MADRS:** (OR 3.86, 95% CI 0.86 to 17.32; Wald $\chi 2$=3.9, p=0.047) Active TBS 56% Sham TBS 25% **% Remission MADRS:** (OR 3.37,95% CI 0.68 to 16.65 Wald $\chi 2$=3.1, p=0.079) Active TBS: 44% Sham TBS: 19% There were no statistically significant differences between the active and sham TBS groups for the HDRS and BDI.	"In conclusion, TBS represents an effective and well-tolerated new option for the improvement of rTMS therapy of major depression that deserves further and more extensive clinical investigation. Not least, the use of TBS facilitates practicability because of the significantly shorter stimulation sessions and lower stimulation intensities." (pg.222)
Randomized Controlled Trial Li et al. 2014[40] Taiwan	**% HDRS change:** (F=6.166; p=0.001) cTBS -22.5% (13.3% - 70.0%) iTBS -42.3% (4.3% to 88.9%) cTBS + iTBS -52.5% (-15.0% to 92.3%) Sham -17.4% (30.0% to -84.6%) **% Responders:** (p=0.010) cTBS 25.0% iTBS 40.0% cTBS + iTBS 66.7% Sham 13.3%	"Our results showed that daily TBS for a period of 2 weeks is a safe and well-tolerated option for antidepressant treatment for patients with TRD and the antidepressant effect is sustainable. As hypothesized, left prefrontal intermittent TBS (Group B or C) was more effective than right prefrontal continuous TBS (Group A) and sham TBS (Group D)" (pg. 2094)
Randomized Controlled Trial Jin et al. 2014[41] United States	**Active vs. Sham sTMS** Response: 53.3% vs. 12.5% (χ^2=7.30, p=0.007) Remission: 11/29 (38%) vs. 1/16 (6%) p=0.015 **Safety**: 40% of patients in the active sTMS group reported feeling light-headed after treatment.	"In this study, a statistically significant decrease in HAMD-17 score was observed in subjects treated with the sTMS device compared to sham. These results indicate that a sub-threshold alternating sinusoidal magnetic field generated in the alpha frequency range can have therapeutic efficacy in patients with MDD." (pg. 4) "The present findings suggest that the sTMS device can be an efficacious treatment for MDD, and supports the conduct of a larger, definitive clinical trial." (pg. 5)

rTMS = repetitive Transcranial Magnetic Stimulation; PTSD = Post-Traumatic Stress Disorder; CI = Confidence Interval; CAPS = Clinician-Administered Posttraumatic Stress Disorder; TRD = Treatment Resistant Depression; LF = Low Frequency; HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; BDI = Beck Depression Inventory; cTBS = continuous Theta-Burst Stimulation; MDD = Major Depressive Disorder

Table A4.3: Summary of Recommendations from Included Evidence-Based Guidelines

Guideline Document	Recommendations
Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS) Lefaucheur et al. 2014[45] Europe	**Summary of Recommendations (pg. 42)** <u>PTSD:</u> "Possible effect of HF rTMS of the right DLPFC in PTSD (Level C)" <u>Depression:</u> "Definite antidepressant effect of HF rTMS of the left DLPFC (Level A)" "Probable antidepressant effect of LF rTMS of the right DLPFC (Level B) and probably no differential antidepressant effect between right LF rTMS and left HF rTMS (Level B)" "No recommendation for bilateral rTMS combining HF rTMS of the left DLPFC and LF rTMS of the right DLPFC" "Definite antidepressant effect of rTMS of DLPFC in unipolar depression (Level A), but no recommendation for bipolar depression " "Antidepressant effect of rTMS of DLPFC is probably additive to the efficacy of antidepressant drugs (Level B) and possibly potentiating (Level C)" "No recommendation for the overall respective antidepressant efficacy of rTMS of DLPFC compared to ECT"
Management of Post-Traumatic Stress Department of Veterans Affairs (VA) and The Department of Defense (DoD) United States 2010[44]	**Summary of Recommendations (pg. 173)** "1. There is insufficient evidence to recommend the use of any of the Biomedical Somatic Therapies for first-line treatment of PTSD. [D]" "2. ECT and rTMS may be considered as an alternative in chronic, severe, medication- and psychotherapy-resistant PTSD. [B]"
Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies Canadian Network for Mood and Anxiety Treatments (CANMAT) Canada 2010[42]	**Summary of recommendations (pg. 17)** "***Part A: Treatment Recommendations*** ***2. Acute phase*** ***a. Choice of an initial treatment modality*** Treatment in the acute phase should be aimed at inducing remission of the major depressive episode and achieving a full return to the patient's baseline level of functioning [I]. Acute phase treatment may include pharmacotherapy, depression-focused psychotherapy, the combination of medications and psychotherapy, or other somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), or light therapy, as described in the sections that follow. Selection of an initial treatment modality should be influenced by clinical features (e.g., severity of symptoms, presence of co-occurring disorders or psychosocial stressors) as well as other factors (e.g., patient preference, prior treatment experiences) [I]. Any treatment should be integrated with psychiatric management and any other treatments being provided for other diagnoses [I]."
Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition American Psychiatric Association (APA) Practice Guidelines United States 2010[43]	**Summary of recommendations (pg. S45)** rTMS: Overall recommendation (Second-line) Acute efficacy: [Level 1] Relapse prevention: [Level 3] Safety and Tolerability: [Level 1] Recommendations for delivery of rTMS (pg.S47) Start with high-frequency rTMS to the left DLPFC. [Level 1] Superior outcome for 20 vs 10 sessions. [Level 2] Minimal evidence for maintenance and relapse prevention effect. [Level 3]

Guideline Document	Recommendations
Depression in adults. The treatment and management of depression in adults. National Institute for Health and Clinical Excellence (NICE) United Kingdom 2009[46]	**Summary of recommendations (pg. 40)** "Recommendation: Current evidence suggests that there are no major safety concerns associated with transcranial magnetic stimulation (TMS) for severe depression. There is uncertainty about the procedure's clinical efficacy, which may depend on higher intensity, greater frequency, bilateral application and/or longer treatment durations than have appeared in the evidence to date. TMS should therefore be performed only in research studies designed to investigate these factors.[18]"

rTMS = repetitive Transcranial Magnetic Stimulation; PTSD = Post-Traumatic Stress Disorder; TRD = Treatment Resistant Depression; HF = High Frequency; LF = Low Frequency; HDRS = Hamilton Depression Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; BDI = Beck Depression Inventory; cTBS = continuous Theta-Burst Stimulation; MDD = Major Depressive Disorder; DLPFC = Dorsolateral Prefrontal Cortex; ECT = Electroconvulsive Therapy; VA/DoD = Veterans Affairs/Department of Defense; CANMAT = Canadian Network for Mood and Anxiety Treatments; APA = American Psychiatric Association