QUERI

Evidence Brief: Factors that Optimize Therapy with Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression

SUPPLEMENTAL MATERIALS

September 2014

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Quality Enhancement Research Initiative
Health Services Research and Development Service
Washington, DC 20420

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LIST OF ABBREVIATIONS

APA: American Psychiatric Association

BD: Bipolar Disorder

DBS: Deep Brain Stimulation

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

ECT: Electroconvulsive Therapy

EPC: Evidence-based Practice Center

ESP CC: VA Evidence-based Synthesis Program Coordinating Center

FDA: Food and Drug Administration

HAMD: Hamilton Rating Scale for Depression

LHF-DLPFC: Left High-frequency Dorsolateral Prefrontal Cortex

MDD: Major Depressive Disorder

OEF: Operation Enduring Freedom

OIF: Operation Iraqi Freedom

PFC: Prefrontal Cortex

PTSD: Posttraumatic Stress Disorder

RCT: Randomized Controlled Trials

RLF-DLPFC: Right Low-frequency Dorsolateral Prefrontal Cortex

RMT: Resting Motor Threshold

RTI-UNC: RTI-University of North Carolina

rTMS: Repetitive Transcranial Magnetic Stimulation

SSRI: Selective Serotonin Reuptake Inhibitor

TRD: Treatment-resistant Depression

VNS: Vagus Nerve Stimulation

SEARCH STRATEGIES

Ovid MEDLINE and OLDMEDLINE (1946 to April Week 2 2014)
Date Searched: April 14, 2014

1	Depressive disorder.mp. or exp Depressive Disorder/
2	transcranial magnetic stimulation.mp. or exp Transcranial Magnetic Stimulation/
3	rTMS.mp.
4	2 or 3
5	1 and 4
6	limit 5 to (english language and humans)
7	limit 6 to (case reports or editorial or letter)
8	6 not 7

Ovid PsycINFO 1806 to April Week 2 2014
Date Searched: April 17, 2014

1	exp major depression/ or (depression or depressive).ti,ab.
2	transcranial magnetic stimulation/ or (rtms or transcranial magnetic stimulation).ti,ab.
3	1 and 2
4	limit 3 to english language
5	limit 4 to human
6	limit 5 to editorial
7	limit 5 to letter
8	6 or 7
9	5 not 8

Ovid EBM Reviews
Date Searched: April 17, 2014

1	(depression or depressive).ti,ab.
2	(rtms or transcranial magnetic stimulation).ti,ab.
3	1 and 2

PEER REVIEW COMMENT DISPOSITION TABLE

Reviewer #	REVIEWER COMMENT	RESPONSE
1. Are the objectives, scope, and methods for this review clearly described?		
1	Yes (*no comments)*	
2	Yes *(no comments)*	
3	Yes (no comments)	
2. Is there any indication of bias in our synthesis of the evidence?		
1	Yes; The review is not done by anyone with clinical neuroscience knowledge to understand critical issues like the physics of TMS and how that interacts with dose questions. Some of the conclusions are thus frankly wrong. Additionally, there is a hubris in thinking that the review can come up with a minimally effective dose, when in fact they cannot. Finally, they rely too heavily on older reviews which relied on earlier studies, and this is thus out of date in many areas, particularly the issue of professional society support and insurance coverage.	Please see related changes detailed below.
2	No *(no comments)*	
3	No (No comments)	
3. Are there any published or unpublished studies that we may have overlooked?		
1	Yes; See my extensive comments at the end with references.	
2	No *(no comments)*	
3	I'd encourage taking a look at the several studies that have examined accuracy of placement of the magnetic stimulation as a potential way to improve outcomes. See, for example, Rusjan PM, Barr MS, Farzan F, Arenovich T, Maller JJ, Fitzgerald PB, Daskalakis ZJ. Optimal transcranial magnetic stimulation coil placement for targeting the dorsolateral prefrontal cortex using novel magnetic resonance image-guided neuronavigation. Hum Brain Mapp. 2010 Nov;31(11):1643-52	Yes, we noted the imaging-guided navigation approach to improving stimulus parameters as a future trend in rTMS research, but that more research is needed in larger samples. We added Rusjan 2010 reference.
4. Please write any additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.		
1	Page 4, line 12. The rMT also helps determine the amount of stimulation needed to get into the cortex, not just minimizing risk. This is important for a comment below about the minimum intensity needed to treat.	Added.
1	Line 21. Manufacturer training shows people how to operate the machine and turn it on and off and who to call if it breaks. It is like the training you get when you buy a car and they show you where the spare tire is hidden. True TMS training is like a driver's license, and the Ford dealer cannot give you that. Training must be done through appropriate non-vendor courses, CME's, offered at annual meetings and at universities. Many insurance companies are requiring non-vendor certification before they will reimburse. The user groups in this area (Clinical TMS Society, World Federation of Societies of Biological Psychiatry Taskforce on Brain Stimulation Therapies) all support non-vendor certification as minimal requirements for practice. VA hospital, for credentialing of TMS, require this non-vendor certification as well.	Changed to, "Training is typically provided by the manufacturer and through appropriate non-vendor courses and certifications required by many insurance companies and health systems, including the VHA."

Reviewer #	REVIEWER COMMENT	RESPONSE
1	The FDA has now revised this limitation based on more data supplied by the manufacturer and the limitation has been lifted (April 2014). See the Neuronetics webpage or do an FDA search to find the new language	Added "In 2014, in response to the results from another multicenter sham-controlled RCT, sponsored by the National Institutes of Health (NIH), the clearance was expanded to include patients who had failed one or more prior antidepressant medications in the current episode."
1	Page 5 line 6. This is an outdated and incorrect statement. The citing of a summary published in 2009, which went back in time and was out of date, ignores new clear guidelines published in the last 5 years. The APA guidelines were published before the NIH large trial was complete. Over the past 5 years all professional societies who have examined the literature have concluded that there is convincing class I evidence of effectiveness in acute depression, and they recommend that it be used. Efficacy and effectiveness are no longer in question. Please see clear recent guidelines published by the WFSBP and others. (1, 2) 1.George MS, Schlaepfer T, Padberg F, Fitzgerald PB. Brain stimulation treatments for depression. World J Biol Psychiatry. 2014;15(2):167-8. doi: 10.3109/15622975.2013.869619. PubMed PMID: 24506290. 2.Schlaepfer TE, George MS, Mayberg H. WFSBP Guidelines on Brain Stimulation Treatments in Psychiatry. World J Biol Psychiatry. 2010;11(1):2-18. Epub 2010/02/12. doi: 10.3109/15622970903170835. PubMed PMID: 20146648. Your discussion of the current status of practice guidelines and position statements did not include consideration of the use of TMS as promulgated in the 3rd Edition of the American Psychiatric Association *Practice Guidelines for the Treatment of Patients with Major Depressive Disorder*, and in other practice guidelines, nor does it reference the current CPT Category I code status. The following authoritative organizations now include TMS Therapy as an established, proven, standard of care treatment option after initial treatment failure with medications. They include the two domestic and two international authorities listed below. • American Psychiatric Association, 2010 *Practice Guidelines for the Treatment of Patients with Major Depressive Disorder* • Agency for Healthcare Research and Quality (2011) • World Federation of Societies for Biological Psychiatry, Schlaepfer, et al, *World J Bio Psych* (2009) • Canadian Network for Mood and Anxiety Treatments, Kennedy, et al. *J Aff Disorders* (2009) The recommendations for the use of TMS in the current APA 2010 *Practice Guidelines for the Treatment of Patients with Major Depressive Disorder,* are clear and unambiguous. Specifically, the document states, "…*for patients whose symptoms have not responded adequately to medication…transcranial magnetic stimulation could also be considered…*".	Changed to "Several professional societies have issued clinical practice guidelines on the use of rTMS for treating depression, including the American Psychiatric Association (APA), World Federation of Societies of Biological Psychiatry Task Force (WFSBP-TF), the Canadian Network for Mood and Anxiety Treatments (CANMAT), the National Collaborating Centre for Mental Health (NCCMH) in the UK, and, most recently, the International Federation of Clinical Neurophysiology. All but the NCCMH regard rTMS as a clinically relevant technique to treat major depression, including treatment-resistant depression. The NCCMH recommends that TMS should only be performed in research studies designed to investigate factors that might increase the procedure's clinical efficacy."

Reviewer #	REVIEWER COMMENT	RESPONSE
1	This review does not reference one of the most recent, authoritative and independent policy papers on the safety and efficacy of TMS, namely the Agency for Healthcare Research and Quality (AHRQ, 2011) report on the comparative effectiveness analysis of non-pharmacologic treatments for treatment resistant depression. That document is significant largely because of its rigorous methodologic approach to study analysis. In that report, the AHRQ Panel concluded that the strength of evidence was "high" for the efficacy of TMS compared to sham treatment. The AHRQ report is also significant for its detailed and thorough analysis of how these outcomes compare to the outcomes expected for medication treatment as an alternative. Specifically, the report summarizes for the reader the likelihood of patient benefit from the standard pharmacologic 'next-step' options. They note for example, that the likelihood of achieving remission in patients with a routine pharmacologic "switch" to next best medication only averaged 22.3% (95% CI: 16.2% to 28.4%). With augmentation, the likelihood of achieving remission was similar, averaging 27.2% (95% CI: 20.4% to 34.0%). These numbers highlight the diminishing benefit with of treating increasing levels of treatment resistance with standard pharmacologic options, and are not as good as the remission rates observed in Neuronetics' Outcomes Study 37.1% (95% CI: 31.8% to 42.8%).	We had previously referenced the associated 2014 Journal of Clinical Psychiatry publication of the 2011 AHRQ review. We added reference to the 2011 Evidence Report as well and added details about the strength of the evidence for response and remission, respectively, as well as a comment about the comparability of rTMS' response and remission rates with other next step pharmacologic options. To better reflect rTMS' balance of benefits and harms, we also added information about the low and insufficient evidence on health outcomes and harms, respectively.
1	Line 27. Again, this is out of date and incorrect. 'Most health plans have decided against…' needs data. In fact, most Medicare subgroups including Palmetto in South Carolina now cover TMS, as do most Blue Cross Blue Shield affiliates. This statement is out of date and needs updating.	Changed to "Insurance coverage of rTMS treatment is mixed, and to help make coverage decisions, several health plans have conducted their own reviews. The BlueCross BlueShield Technology Assessment Program published an updated assessment on the effect of TMS therapy on depression in early 2014. The assessment relied on results from 2 published trials, FDA documents, extension studies, and 7 meta-analyses, and concluded that, while the mechanism by which TMS might improve depression is biologically plausible, large trials and meta-analyses do not provide convincing evidence of improved health outcomes. In 2013, United Healthcare published a medical policy on TMS that stated "there is insufficient evidence that transcranial magnetic stimulation (TMS) is beneficial for health outcomes in patients with major depression." Anthem (Wellpoint) covers rTMS for major depression with one of the 2 FDA-cleared devices for patients meeting very strict criteria. CMS has not issued a coverage policy on rTMS, however a number of Medicare contractors have issued Local Coverage Determinations regarding rTMS coverage. Cahaba Government Benefit Administrators®, LLC (L32834), Palmetto GBA *(continued)*

Reviewer #	REVIEWER COMMENT	RESPONSE
		(Continued) (L34170), Novitas Solutions, Inc. (L32055 and L33660), and First Coast Service Options, Inc. (L33676) cover rTMS for patients diagnosed with resistant depression with some requirements on the definition of resistance and limitations on which patients can safely receive rTMS treatment. Conversely, National Government Services, Inc. (L32038), Wisconsin Physicians Service Insurance Corporation (L32220), and Noridian Healthcare Solutions, LLC (L33495) have issued non-coverage policies, concluding that rTMS is not medically necessary."
2	Impressive accomplishment in a brief period of time. In the Background (P. 3, lines 23-33): While there is no national consensus on Medicare coverage nationally, regional coverage has fluctuated. I would confirm the current status of CMS coverage in various sections of the country.	Thank you. Changed to, "CMS has not issued a coverage policy on rTMS, however a number of Medicare contractors have issued Local Coverage Determinations regarding rTMS coverage. Cahaba Government Benefit Administrators®, LLC (L32834), Palmetto GBA (L34170), Novitas Solutions, Inc. (L32055 and L33660), and First Coast Service Options, Inc. (L33676) cover rTMS for patients diagnosed with resistant depression with some requirements on the definition of resistance and limitations on which patients can safely receive rTMS treatment. Conversely, National Government Services, Inc. (L32038), Wisconsin Physicians Service Insurance Corporation (L32220), and Noridian Healthcare Solutions, LLC (L33495) have issued non-coverage policies, concluding that rTMS is not medically necessary."
2	In the Scope, allowing studies employing a large variation of TRD definitions, while understandable, is a key factor that might limit findings, because the heterogeneity can mask effects. This point needs to be more clearly made in the Discussion as a limitation, and its implications need to be discussed.	Added "Another major limitation is the heterogeneous definition of TRD throughout the literature on rTMS treatment for depression. We included studies that used a variety of definitions of TRD, which may have affected the conclusions in this report and lessened the apparent benefit of rTMS. If the VA wishes to evaluate their own data on rTMS, a uniform definition of TRD should be adopted."

Reviewer #	REVIEWER COMMENT	RESPONSE
1	Page 10, Line 8. Well, this certainly shows how simply doing meta-analyses can stand in the way of scholarship. There is a great deal known about how age influences TMS antidepressant outcome, none of which is mentioned in this evidence-based synthesis. I will attempt to summarize it here. In the early days of TMS studies, the FDA was quite concerned about potential harm of TMS, particularly seizures. We knew that the risk of seizures was a function of a matrix of TMS intensity, frequency, train duration, and inter-train interval. (3) The FDA thus limited us to treating at or below the motor threshold. Realize that the motor threshold is determined over the motor cortex while we treat over the prefrontal cortex. In the early studies with low intensity, no one over 50 responded to TMS. (4) We wondered if there might be selective prefrontal atrophy in depressed patients as they aged, and in fact found this was so, and then determined the needed MT for actually reaching the prefrontal cortex and overcoming this atrophy. This was 117% of MT, rounded up to 120. We then carried this out in an elderly depressed group and found that it worked. (5-7) Most studies since that time have used intensities at least 120%MT. For patients over 80, or who may have comorbid conditions that cause atrophy (like past substance abuse, alzheimer's disease, etc), the intensity may need to be greater than 120% MT. It is incorrect to state that 100%MT works, as it does not for anyone over age 50. In summary, now that we know about the minimum intensity needed to reach the brain in older adults, age does not seem to be a predictor, **at intensities at least 120%.** But the caveat is that most studies did not include the typical VA population with many comorbidities and past substance abuse. Veterans may need even higher intensities. A Merit grant coordinated with CSP 556 is examining this question directly. (PI Allyson Rosen, Palo Alto VA) 3. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop in the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalography and Clinical Neurophysiology. 1998;108:1-16. 4. Figiel GS, Epstein C, McDonald WM, Amazon-Leece J, Figiel L, Saldivia A, et al. The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. Journal of Neuropsychiatry & Clinical Neurosciences. 1998;10(1):20-5. 5. Nahas Z, Li X, Kozel FA, Mirzki D, Memon M, Miller K, et al. Safety and benefits of distance-adjusted prefrontal transcranial magnetic stimulation in depressed patients 55-75 years of age: a pilot study. Depress Anxiety. 2004;19(4):249-56. Epub 2004/07/27. doi: 10.1002/da.20015. PubMed PMID: 15274174. 6. McConnell KA, Nahas Z, Shastri A, Lorberbaum JP, Kozel FA, Bohning DE, et al. The transcranial magnetic stimulation motor threshold depends on the distance from coil to underlying cortex: a replication in healthy adults comparing two methods of assessing the distance to cortex. Biol Psychiatry. 2001;49(5):454-9. Epub 2001/03/29. http://www.ncbi.nlm.nih.gov/pubmed/11274657. PubMed PMID: 11274657. 7. Kozel FA, Nahas Z, deBrux C, Molloy M, Lorberbaum JP, Bohning D, et al. How coil-cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. J Neuropsychiatry Clin Neurosci. 2000;12(3):376-84. Epub 2000/08/24. http://www.ncbi.nlm.nih.gov/pubmed/10956572. PubMed PMID: 10956572.	We thank the reviewer for suggesting additional citations related to age. Figel 1998 and Nahas 2004 met our eligibility criteria and were added to the report. In Key Question on adequate course of treatment added qualifications to statement that 100% RMT works primarily in patient under 50 years of age without Axis I comorbidities and past substance abuse.

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1	In terms of predictors of response, TMS is like all other antidepressants. Higher levels of treatment resistance have consistently correlated with poorer outcomes. Additionally, comorbid anxiety disorders, or anxiety symptoms, predict poorer response. See Lisanby (8)et al. 8. Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2009;34(2):522-34. doi: npp2008118 [pii] 10.1038/npp.2008.118 [doi]. PubMed PMID: 18704101.	We thank the reviewer for suggesting additional evidence about predictors of response. Since our report focuses on response and remission outcomes, rather than pre- to post-treatment changes in depression scores, Lisanby 2009 did not meet our eligibility criteria.
2	In Results, I'm a little confused by the comorbidity results on p.11, lines 21-25. It looks like the Partial Hospitalization Program and PTSD Clinic population involved patients with MDD or PTSD, although it might be that patients with PTSD "who remained depressed" indicates comorbid depression. The authors should be clearer about this part.	Changed to, "One trial from the Partial Hospitalization Program and Post Traumatic Stress Disorder Clinic of the Mental Health Service Line at the Department of Veterans Affairs Medical Center in Washington, DC included 12 patients with TRD and combat PTSD who remained depressed after a minimum of one month on antidepressant therapy (100% male; mean age of 55 years). After 2 weeks of fast (5 Hz) and slow (1 Hz) frequency left-sided rTMS, response rates were 67% and 83%, respectively."
2	In Results, lines 8 and 10, I think the reference, listed as # 15 in two places, should be # 16.	Corrected.
1	Page 14 conmeds. Most of the early studies required that patients be antidepressant medication free as this was scientifically simpler in assessing whether TMS worked or not, without having to worry about medication interactions. The overall response and remission rates in the two large modern RCT's were 15% in the double blind phase (3 or 4 weeks) and then 30% remission in the active open at 6 weeks. In contrast to this 30% remission at 3-4 weeks in the medication free studies, the Carpenter open label study found remission rates much higher and an overall response rate of about 60%. Many people use these studies to suggest that TMS rates on patients with medications would likely be higher than the medication free initial studies. This has clearly been shown to be the case with ECT for example (see Sackeim, 2010) The Synthesis is correct in that this has not been formally studied.	We appreciate the reviewer's confirmation of our synthesis of the effects of concomitant medications.
1	Page 15, line 23. The NIH trial did not use the same protocol as Neuronetics, and did not confirm it as they were conducted simultaneously. The NIH trial randomized patients and stratified based on treatment resistance. Moreover it was for a fixed 3 week course, with continued treatment for those showing improvement. The NIH trial was the first truly double-blinded study, with an active sham and clear documentation of the integrity of the blind.	Corrected.

Reviewer #	REVIEWER COMMENT	RESPONSE
1	See this reference for quality of life data from the neuronetics pivotal study. (9)M. A.</author><author>Lisanby, S. H.</author></authors></contributors><auth-address>Department of Psychiatry, Stanford University Medical Center, Stanford University, 401 Quarry Road, Palo Alto, CA 94305 USA. Electronic address: solvason@mac.com.
University of Texas Southwestern Medical School, Dallas, TX, USA.
The Alfred Hospital, Melbourne, Australia.
Medical College of Georgia, Augusta, GA, USA.
Wake Forest University, Winston-Salem, NC, USA.
Northwestern University, Chicago, IL, USA.
Neuronetics, Inc., Malvern, PA, USA.
Duke University, Durham, NC, USA.</auth-address><titles><title>Improvement in Quality of Life With Left Prefrontal Transcranial Magnetic Stimulation in Patients With Pharmacoresistant Major Depression: Acute and Six Month Outcomes</title><secondary-title>Brain Stimul</secondary-title><alt-title>Brain stimulation</alt-title></titles><alt-periodical><full-title>Brain stimulation</full-title><abbr-1>Brain Stimulat</abbr-1></alt-periodical><edition>2013/12/18</edition><dates><year>2013</year><pub-dates><date>Nov 4</date></pub-dates></dates><isbn>1935-861X (Electronic This needs to be in the review. 9. Solvason HB, Husain M, Fitzgerald PB, Rosenquist P, McCall WV, Kimball J, et al. Improvement in Quality of Life With Left Prefrontal Transcranial Magnetic Stimulation in Patients With Pharmacoresistant Major Depression: Acute and Six Month Outcomes. Brain Stimul. 2013;10.1016/j.brs.2013.10.008. Epub 2013/12/18. doi: 10.1016/j.brs.2013.10.008. PubMed PMID: 24332384.	Added.
1	Page 19, line 31 adequate dose. This section is naïve about TMS and ignores the substantial translational clinical work done with TMS in the motor system, where one can stimulate and see immediate movements in the opposite body, and measure changes in cortical inhibition or excitability. It also ignores the brain imaging (PET, SPECT, fMRI) work where surrogate markers of brain activity have been used to infer the minimum dose needed to interact with brain circuits.	We are aware of the brain imaging work and agree that the surrogate markers of brain activity are on the causal pathway to clinical outcomes. However, since this report is focused only on the final clinical outcomes, we did not include the evidence on surrogate markers.
1	Line 38 The fact that 100% MT works is not due to sample size, but physics!! See the discussion above about the body of work showing why you need at least 100% MT in most adults, and 120% MT in anyone with atrophy or over age 50.	Removed statement about sample size and added qualification that intensities down to 100% RMT were effective primarily in patient under 50 years of age without Axis I comorbidities and past substance abuse.
1	Line 39 This is a logical fallacy and is not correct. The minimum intensity for which there are class I data is 120% MT. There are no supportive data less than this.	Added, “The best evidence from 2 large multicenter RCTs supports using 120% RMT to guarantee an adequate stimulation intensity. Using data from the 2014 systematic review by Berlim and colleagues of 29 sham-controlled trials of high-frequency left-sided PFC rTMS at lower intensities, 80% to 110%, we found that intensities down to 100% may also be effective in patients primarily under 50 years of age without Axis I comorbidities and past substance abuse.”

Reviewer #	REVIEWER COMMENT	RESPONSE
1	Page 20, line 11 This is incorrect. The only large Class I trials used 120% MT for 4-6 weeks. Any dose less than this is inadequate. The statistical logic behind starting with an inadequate dose based on small inadequate trials baffles me. If fluoxetine were being analyzed this way, they would suggest 5 mg for 2 weeks to start. This would clearly be inadequate, and waste much time and effort and promote dropouts due to non-response. As an expert in the field the statement on line 13 that an underdosed prescription is a 'reasonable place to start' is not scientifically correct and is not justified and is bad medicine. This should not be a statement in the final synthesis. Imagine recommending systematic underdosing of an antibiotic, allowing the infection to continue growing and patients to suffer. There are no data to support the incorrect speculation of line 13, and lots of studies to show this is an inadequate dose.	Deleted.
1	Line 16. There are no data to support that what is written here is a 'minimally effective dose.' This should be stricken. The minimally effective dose is that which was approved by the FDA and tested in two large RCT's.	Deleted
1	Page 22 long-term durability. For proper interpretation, this section needs to note that the current treatments for depression have poor long term durability, with the exception of vagus nerve stimulation where long-term durability is high. For example, from the STAR*D medication study, in patients who did not respond to the first two levels, only 20% of eventual remitters remained remitted after 12 months. ECT has >50% relapse rates at 6 months. The small studies with TMS suggest durability that is at least as good as other treatments for this population.	Added: "For patients with TRD, response to ECT or various antidepressant medications is often transient."
1	Page 25 line 22 Again, the suggestion that there is 'low-strength evidence' that 10 treatments at 10% RMT is incorrect. Low-strength evidence means no strength evidence and that it has not been scientifically proven. This conclusion is not based on data, or the scientific method, and should be removed. The only minimally effective doses are those that have been shown effective in large RCT, and are FDA approved. Publishing this statement would be tantamount to malpractice, and should not be in the final conclusions.	Changed to: "To guarantee adequate stimulation, 2 large multicenter RCTs support using standard rTMS at 10 Hz, 120% RMT, 3,000 pulses per session, 5 days per week for 3 to 6 weeks. Intensities down to 100% may also be effective in patients primarily under 50 years of age without Axis I comorbidities and past substance abuse."
1	Page 27 line 41 – response and remission rates in open label trials on medications with comorbidities are in the 50-60% range, for treatment resistant depressed patients. This is better than stage III in the STAR*D studies, and approaches modern ECT outcomes.	Changed to: "In summary, rTMS represents a wide spectrum of treatments, many variations of which are still not well-studied. The specific LHF-DLPFC protocols cleared by the FDA have the strongest evidence of efficacy, with response and remission rates that are at least as good or better than those in the third and fourth acute treatment steps in the STAR*D trial, as well as improvements in quality of life, and no major safety concerns have been uncovered."
1	Page 27, Line 42. The RCT's were done on patients off medications. More recent trials on medications show much better response. ECT done on antidepressant medication free patients has worse outcomes than ECT on patients who maintain their antidepressants (Sackeim, 2011).	The RCT's are mixed in terms of whether the patients were on or off medications and clear differences have not yet been found based on whether rTMS is used as augmentation.

Reviewer #	REVIEWER COMMENT	RESPONSE
1	Page 27, Line 43. See above, there have been studies showing improvement in quality of life. This conclusion is not correct	Changed to: "The specific LHF-DLPFC protocols cleared by the FDA have the strongest evidence of efficacy, with response and remission rates that are at least as good or better than those in the third and fourth acute treatment steps in the STAR*D trial, as well as improvements in quality of life, and no major safety concerns have been uncovered."
2	In their summary, I think the authors understate the potential benefit of rTMS in TRD patients (p. 27, lines 39-43). TRD is hard to treat. From STAR*D findings, after you've failed two good antidepressant trials, the likelihood of remission is 15% or lower. Compared to these outcomes, a remission rate range of 19-35% looks more promising, so I think their categorization of rTMS rates as being "modest" needs to be placed in perspective of these rates in TRD patients otherwise being worse. I think their results more strongly support considering the use of rTMS in this TRD VA population than their summary indicates.	Changed to, "The specific LHF-DLPFC protocols cleared by the FDA have the strongest evidence of efficacy, with response and remission rates that are at least as good or better than those in the third and fourth acute treatment steps in the STAR*D trial, as well as improvements in quality of life, and no major safety concerns have been uncovered."
2	Also, I think the evidence of limited adverse events so far for rTMS is important to emphasize more in the context of TRD, especially as the gold standard treatment for TRD presented here is ECT (which can be harder to tolerate and has more clearly described adverse events). This point may be especially relevant to a VA TRD population, which has higher rates of comorbid traumatic brain injury and potentially more contraindications to ECT treatment.	Changed to, "In the meantime, rTMS has acceptable acute efficacy, and, compared to ECT, rTMS is less invasive, has a safety advantage for some patients, and may have more comparable benefits in TRD patients than originally thought."
1	Page 28 line 3. This is a healthcare economics statement. These data were not presented in the review. In fact, in non-VA settings, TMS is quite cost-effective. (10) 10. Simpson KN, Welch MJ, Kozel FA, Demitrack MA, Nahas Z. Cost-effectiveness of transcranial magnetic stimulation in the treatment of major depression: a health economics analysis. Adv Ther. 2009;26(3):346-68. Epub 2009/03/31. doi: 10.1007/s12325-009-0013-x. PubMed PMID: 19330495.	Deleted
1	Page 28, Line 6. This is a bizarre statement, totally lacking any supporting data. There are no data about TMS response rates in patients who have failed or could not tolerate ECT. ECT is only minimally used in the VA system, for a variety of reasons, including scheduling recovery room time, cognitive side effects, medical comorbidities and stigma. None of these are problems with TMS. Most healthcare systems are using TMS as a second line treatment after some level of medication failure, and BEFORE ECT. That is the population that has been studied and for which there is evidence of effectiveness and for which it is FDA approved. Concluding a synthesis with a totally heretical and unsupported speculation seems unwise and detracts from the many more reasoned conclusions within the body of work.	Changed to, "In the meantime, rTMS has acceptable acute efficacy, and, compared to ECT, rTMS is less invasive, has a safety advantage for some patients, and may have more comparable benefits in TRD patients than originally thought."
2	The authors could emphasize more the potential importance of researching how rTMS might play a role in MDD/PTSD comorbidity in the VA population.	Regarding the VA Cooperative Study that is currently enrolling participants, we added, "The results from this study may answer many outstanding questions regarding the use of rTMS among TRD patients with comorbidities."

Reviewer #	REVIEWER COMMENT	RESPONSE
2	An important general point, implied throughout but never clearly stated, is that rTMS is really a general approach rather than a specific entity, and that researchers, clinicians, and patients are early on in understanding how to most effectively apply this spectrum of treatments. Overall, however, I found this to be an excellent, thoughtful, and comprehensive report.	On page 4 we added: "TMS encompasses a wide spectrum of treatments. Aside from a single TMS stimulation, repetitive TMS, and deep TMS, strategies for using rTMS vary based on types of coils, region of the brain stimulated (*ie*, left or right dorsolateral prefrontal cortex, or bilateral), "dose" (*eg*, intensity, percent of resting motor threshold (%RMT)), speed of pulses (*ie*, Hz, pulses per second), pulse train duration, inter-train interval, trains per session, total number of pulses, number of weekly sessions, duration (*ie*, 2 to 6 weeks), and total number of sessions."
3	I thought the report side stepped comparisons with ECT to too much of an extent. Specifically, there is good reason to extrapolate from meta-analyses and more contemporary RCTs that TMS is substantially less effective that ECT across 4-6 weeks, but TMS has some advantages concerning tolerability (i.e., lack of significant cognitive side effects) and medical safety (it does not require general anesthesia). There does not need to be an adequately powered RCT to accept the notion that the treatment that requires 6-12 administrations of general anesthesia is more dangerous than the one that does not! ECT is not even available at the Philadelphia VAMC – we have to refer out for this treatment when it is urgently indicated.	Added to Background: "The American Psychiatric Association (APA) recommends ECT as a treatment of choice for patients with severe MDD that is not responsive to psychotherapeutic and/or pharmacological interventions.[20] The recommendation was based on older meta-analyses of clinical trials which found remission rates of 70% to 90% for major depression and demonstrated that ECT is more effective and works faster than other therapies with which it has been compared, including rTMS.[21,22] Although a 2014 meta-analysis confirmed these older findings about the superiority of ECT for severe or resistant major depression *overall*,[23] findings from other recent meta-analyses that focused exclusively on TRD suggest there may be less of a difference between ECT and rTMS in TRD subgroups in response (range, 20% to 64% vs 20% to 58%) and remission (range, 15% to 53% vs 9% to 43%).[14,24,25] ECT requires general anesthesia and is associated with transient episodes of hypertension, tachycardia, and arrhythmia, is still socially stigmatized, has high relapse rates (> 60%), and, in a community-based setting, may have more modest remission rates than expected.[26]" Changed conclusion to: "In the meantime, rTMS has acceptable acute efficacy, and, compared to ECT, rTMS is less invasive, has a safety advantage for some patients, and may have more comparable benefits in TRD patients than originally thought."

Reviewer #	REVIEWER COMMENT	RESPONSE
5. Are there any VA clinical performance measures, programs, quality improvement measures, patient care services, or conferences that will be directly affected by this report? If so, please provide detail.		
1	*no response*	
2	Not that I know of.	
3	I can't think of any that aren't already mentioned in the report.	
4	I'd begin accepted that the FDA has approved several TMS devices (i.e., it is a "proven" treatment in the eyes of the most important regulatory authority), but that – outside of the specific protocols that were accepted by the FDA as pivotal trials - the parameters of administering the treatment are not well-studied and there is real reason to be skeptical about the relative effectiveness and cost-effectiveness of this treatment. Given the difficulty of implementing a 5 day per week intervention within most VAMC, it would behoove us to take these implementation issues – including questions of dose-response and maintenance of gains following the first 4-6 weeks of treatment – very seriously! I likewise would encourage a "call to action" regarding monitoring outcomes after treatment – there is great need to determine the durability of TMS response.	Added to the Discussion: "In summary, rTMS represents a wide spectrum of treatments, many variations of which are still not well-studied. The specific LHF-DLPFC protocols cleared by the FDA have the strongest evidence of efficacy, with response and remission rates that are at least as good or better than those in the third and fourth acute treatment steps in the STAR*D trial, as well as of improvements in quality of life, and no major safety concerns have been uncovered. However, nearly all of this evidence was developed in experimental settings. Also, decisions to use rTMS must be weighed by consideration of the uncertainty about the maintenance of its benefits beyond the first 4-6 weeks of treatment and of the potential difficulty of implementing a 5-day per week intervention. The current VA/DoD Clinical Practice Guidelines (2009) support ECT as the recommended somatic treatment strategy for patients who have failed multiple other treatment strategies on management of Major Depressive Disorder and does not address rTMS.[101] Since the sections of the 2009 VA/DoD CPG on MDD management appear outdated in their statement that TMS is not FDA-approved, we suggest the VA/DoD update the CPG to consider the two FDA clearances and the AHRQ findings of high-strength evidence about rTMS' acute efficacy that have emerged since 2009. In the meantime, rTMS has acceptable acute efficacy, and, compared to ECT, rTMS is less invasive, has a safety advantage for some patients, and may have more comparable benefits in TRD patients than originally thought." Also added to the list of recommended objectives for future research. "As there is a great need to determine the durability of rTMS response, monitoring of outcomes after treatment should be included in this effort."

Reviewer #	REVIEWER COMMENT	RESPONSE
6. Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.		
1	See below. I would be glad to re-review if that would help.	
2	Unsure.	
3	None come to mind	

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EVIDENCE TABLES

QUALITY ASSESSMENT OF INCLUDED MULTICENTER TRIALS

Author Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of participants, personnel and outcome assessors?	Formal assessment of adequacy of the blind?	Incomplete outcome data adequately addressed?	Study reports free of suggestion of outcome reporting bias?	Study free of other sources of bias?	Risk of bias?
George 2010	Unclear.	Unclear.	Yes.	Yes.	Yes.	Yes.	Yes.	Low.
O'Reardon 2007	Unclear.	Unclear.	Yes.	No.	Yes.	Yes.	Unclear.	Unclear.
Fitzgerald 2006	Yes.	Unclear.	Yes.	No.	Yes.	Yes.	Yes.	Low.
Fitzgerald 2011	Yes.	Unclear.	Yes.	No.	Unclear.	Yes.	Yes.	Low.

QUALITY ASSESSMENT OF INCLUDED SYSTEMATIC REVIEWS

Author Year	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?
Berlim 2013	Can't answer.	Can't answer.	Yes.	Yes.	Yes.	Yes.	Unclear, not documented.	No.	Yes.	Yes.	Yes.
Berlim 2014	Can't answer.	Can't answer.	Yes.	Yes.	Yes.	Yes.	Unclear, not documented.	Yes.	Yes.	Yes.	Yes.
Berlim 2013	Can't answer.	Can't answer.	Yes.	Yes.	Yes.	Yes.	Unclear, not documented.	No.	Yes.	Yes.	Yes.
Gaynes 2014	Can't answer.	Yes.	Yes.	No.	Yes.	Yes.	Yes.	Yes.	Yes.	Yes.	Yes.
UofC 2014	Can't answer.	Yes.	Yes.	No.	Yes.	Yes.	Yes.	No.	Yes.	Yes.	Yes.

ONGOING CLINICAL TRIALS

Identifier	Sponsor	Title	Status
NCT01583023	McGill University Health Center	Assessing the efficacy of left repetitive transcranial magnetic stimulation (rTMS) as an adjunctive treatment to mood stabilizers for the treatment of bipolar depression	Not recruiting
NCT01515215	Centre for Addiction and Mental Health	Repetitive transcranial magnetic stimulation (rTMS) for treatment resistant depressive disorder	Not recruiting
NCT01516931	Xijing Hospital	A study to evaluate the efficacy of repetitive transcranial magnetic stimulation in the prevention of relapse of the symptoms of depression	Recruiting
NCT01409317	Douglas Mental Health University Institute	Neural predictors and longitudinal neural correlates of clinical improvement after standard or deep transcranial magnetic stimulation in major depression: A randomized study	Enrolling by invitation
NCT01162382	Washington University School of Medicine	Repetitive transcranial magnetic stimulation (rTMS) for the treatment of major depressive disorder: A functional connectivity magnetic resonance imaging (fcMRI) study	Suspended-undergoing changes
NCT01677078	Rennes University Hospital	Assessment of the neuronavigation system coupled with repetitive transcranial magnetic stimulation. A randomized double blind study	Recruiting
NCT01900314	University of Michigan	Imaging biomarkers for TMS treatment of depression	Recruiting
NCT02029963	University of Manitoba	The efficacy of repetitive transcranial magnetic stimulation in relapse prevention of major depressive disorder	Enrolling by invitation
NCT02125799	Douglas Mental Health University Institute	A pilot trial on the effectiveness and tolerability of accelerated high frequency repetitive transcranial magnetic stimulation for treating resistant major depression	Enrolling by invitation
NCT02123485	University of Aarhus	The antidepressant efficacy of repetitive transcranial magnetic stimulation (rTMS) as add-on to electroconvulsive therapy (ECT). A double blind randomized controlled trial	Not recruiting
NCT01887782	Centre for Addiction and Mental Health	A randomized controlled study of conventional versus theta burst repetitive transcranial magnetic stimulation in the treatment of major depressive disorder	Recruiting
NCT01191333	Department of Veterans Affairs	CSP #556 - The effectiveness of rTMS in depressed VA patients	Recruiting
NCT01860157	Centre for Addiction and Mental Health	A randomized controlled study of H1-coil rTMS for treatment-resistant late-life depression	Recruiting
NCT02042573	Centre Hospitalier Universitaire Dijon	TMSFOS: Preliminary study to investigate the effect of rTMS and SSRI antidepressants on leukocyte expression of the C-FOS and DUSP1 genes in patients treated for depression	Recruiting
NCT02016456	Institute of Mental Health Nottingham	Transcranial magnetic stimulation to treat depression	Not recruiting
NCT01829165	Stanford University	A causal neural network-level understanding of depression and its treatment through concurrent TMS and fMRI	Recruiting
NCT02080507	Emory University	rTMS in Treatment Resistant Depression	Recruiting

UNPUBLISHED CLINICAL TRIALS

Identifier	Sponsor	Title	Comparisons	Enrollment	No. of Centers	Date Completed	Potential Publication Matches
NCT00186784	St. Joseph's Healthcare Hamilton	Repetitive transcranial magnetic stimulation (rTMS) in unipolar depression	(1) LHF+RLF (2) LHF+R-sham (3) L-sham+RLF (4) R-sham+L-sham	21	1	July 2011	None
NCT00018746	Department of Veterans Affairs	Efficacy of threshold vs. subthreshold TMS in the treatment of depression	(1) Active rTMS (2) Sham	NR	1	July 2001	Boutros (2002)[1]
NCT01240083	University of Regensburg	Effectiveness of theta-burst stimulation (TBS) versus tonic high frequency repetitive transcranial magnetic stimulation (rTMS) in patients with major depression	(1) R-DLPFC continuous TBS + L-DLPFC intermitted TBS (2) LF R-DLPFC + HF L-DLPFC (3) R-sham + L-sham	61	1	October 2011	None
NCT00168272	Alfred Psychiatry Research Centre	A randomised double-blind trial of low and high frequency stimulation rTMS (repetitive transcranial magnetic stimulation) in major depression	(1) Active priming RHF + RLF (2) R-Sham priming + RLF	100	1	March 2007	Fitzgerald (2008)[2]
NCT0115699	Mayo Clinic/ Neuronetics	Study of repetitive transcranial magnetic stimulation (rTMS) as adjuvant treatment for depression	Open label	2	1	Terminated – funding and slow recruitment	

Potential Publication Matches

1. Boutros NN, Gueorguieva R, Hoffman RE, Oren DA, Feingold A, Berman RM. Lack of a therapeutic effect of a 2-week sub-threshold transcranial magnetic stimulation course for treatment-resistant depression. *Psychiatry Res.* Dec 30 2002;113(3):245-254.

2. Fitzgerald PB, Hoy K, McQueen S, et al. Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol.* Feb 2008;28(1):52-58.