Washington State Health Care Authority

Transcranial Magnetic Stimulation for Treatment of Selected Behavioral Disorders

Peer review and public comment on draft evidence report

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Health Technology Assessment Program (HTA)

Washington State Health Care Authority

PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126
www.hca.wa.gov/hta
shtap@hca.wa.gov

Prepared by:
RTI International–University of North Carolina Evidence-based Practice Center
Research Triangle Park, NC 27709
www.rti.org

This document was created in response to peer review and public comments on a Draft Health Technology Assessment (HTA) report prepared by the RTI-UNC Evidence-based Practice Center through a contract to RTI International from the State of Washington Health Care Authority (HCA). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the State of Washington HCA and no statement in this document should be construed as an official position of the State of Washington HCA.

The information in the document is intended to help the State of Washington's independent Health Technology Clinical Committee make well-informed coverage determinations. This document and its associated Evidence Report are not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this document and the associated Evidence Report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

Acknowledgments

The following individuals contributed to the report associated with this document:
Lead Investigator: Shivani Reddy, MD, MS
Co-Investigators: Leila Kahwati, MD, MPH; Shannon Kugley, MS; Colleen Ovelman, BA; Valerie Ng, BS; Caroline Rains, MPH
Clinical Advisor: Bradley Gaines, MD, MPH
Project Coordinator: Caroline Rains, MPH
Scientific Reviewer: Gerald Gartlehner, MD, MPH
Library/Document Preparation: Mark Howell, MLS

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Peer Review Comments and Responses

Two independent, external peer reviewers were invited to provide comments on the Draft Evidence Report and were provided with an honorarium for their review. The peer reviewer's name, affiliations, and conflicts of interest are reported in ***Table 1***.

Table 1. External Peer Reviewer of the Draft Evidence Report

Name	Title/Affiliation	Summary of Conflicts of Interest Reported
John W Williams Jr, MD, MHS (Reviewer 1)	Duke University Department of Medicine	Financial conflicts: None. Non-financial conflicts: Peer reviewer has a primary clinical specialty of general internal medicine. He has authored many publications on treatment for depressive disorder but none specifically focused on TMS.
F. Andrew Kozel, M.D., M.S.C.R. (Reviewer 2)	Florida State University Department of Behavioral Sciences and Social Medicine	Financial conflicts: Peer reviewer receives grant support from NIMH for a co-investigator role on a TMS project. Non-financial conflicts: Peer reviewer has a primary clinical specialty of psychiatry and has authored publications related to the topic area. Peer reviewer is a psychiatry consultant on a Department of Defense TMS project (no salary support per VA rules). Peer reviewer is the co-chair of the TMS Society Clinical Standards Committee, though the committee has not made a statement on the areas indicated in this review.

The peer reviewers did not identify any missing studies and did not identify any studies that should have been excluded from the report. We addressed many of the comments submitted by the reviewers in the Final Evidence Report; though some comments or suggestions were outside the scope of the HTA. We considered the revisions made based on peer review comments as minor revisions. Specific peer review comments and responses are provided in ***Table 2***.

Table 2. Peer Reviewer Comments on Draft Evidence Report and Response

Item	Comment	Response
Introduction		
Are there any additional issues you think we should cover in the introduction?	Reviewer 1: Consider adding the typical number of sessions and/or duration of treatment. Also consider addressing whether there is a theoretical basis to think that the different types of TMS may differ in efficacy. Reviewer 2: 1.4 Technology Description – should make clear that TMS should be prescribed and monitored by a physician who has adequate training in the disease condition being treated (e.g., severe treatment resistant depression), the safe and effective use of the TMS device, knows the evidence for indications as well as medical and psychiatric contraindications, current FDA status of the treatment being offered, and relevant neuroscience. Would make explicit that dTMS and TBS are subsets of rTMS. The use of rTMS in this context appears to indicate only standard pattern 1 Hz, 5, Hz, 10 Hz, 20 Hz, etc .	We have added text to section 1.4 of the report to address the concerns of both reviewers.

Do you see anything inaccurate, superfluous, or unclear?	Reviewer 1: No Reviewer 2: Page 3 – 1.4 – line 3 - physician present on site – Whether there is physician on-site or available to be immediately contacted depends on the level of training of the TMS treater. Page 3 – 1.4 – line 7 and 8 – "Safety protocols include offering … having anti-epileptics and oxygen on hand" is inaccurate. There is no standard or need to have anti-epileptics or oxygen on hand. Even in the very rare occurrence of a seizure, all have been self-limited and thus there is not need for oxygen or anti-epileptic medications. Page 3 – 1.4 – not sure why showing one manufacturer's device Page 3 – 1.4 – line 9 – the device that is placed on the patient's scalp is more typically referred to as a "coil" and not a "wand." Page 3 – 1.4 – bottom (1) – "high frequencies (>1 Hz, usually 10 to 20 Hz) stimulate neurologic activity and low frequencies (<1Hz) inhibit activity" s/b "high frequencies (>1 Hz, usually 5, 10, or 20 Hz) stimulate neurologic activity and low frequencies (≤1Hz) inhibit activity." Also, should mention the impact on cortical excitement is in general and can vary across individuals. Page 3 – 1.4 – bottom (2) – "resting motor potential or minimum activity to evoke a motor response in a small muscle of the hand" typically referred to as "motor threshold" and is defined as amount of energy to produce visible twitch (or EMG minimum) 50% of the time Page 4 – 2nd paragraph- line 2 – again there is No requirement for Oxygen or Anti-epileptic medications to be available Page 4 -2nd paragraph- line 2 - should clarify only one study demonstrated temporary hearing loss – multiple studies have demonstrated that wearing hearing protection prevents hearing loss Page 4 – 1.5 – first line. Minor but the first TMS devices were not initially submitted for FDA clearance Page 5 - The Food and Drug Administration (FDA) has cleared NeuroStar® Advanced Therapy for Mental Health as an adjunct in the treatment of adults with obsessive-compulsive disorder (OCD).	We have made revisions to sections 1.4 and 1.5 of the report to address the concerns of Reviewer 2. Additionally, we have added text to the legend of Figure 1 to indicate the image is an illustrative example and not an endorsement of the specific device shown in the image, as well as updated Table 1 to include NeuroStar® Advanced Therapy for Mental Health updated indication for OCD.

Any additional comments?	Reviewer 1: No Reviewer 2: Overall, this is a very nicely written background indicating the public health crisis represented by the disorders: generalized anxiety disorder (GAD); obsessive-compulsive disorder (OCD); major depressive disorder (MDD); posttraumatic stress disorder (PTSD); smoking cessation; and substance use disorder (SUD). The degree of disease burden and critical need for additional treatments impacts many of my comments in the sections below.	Thank you.
Methods		
Do you see any problems with our methods?	Reviewer 1: Long-term or late-emerging adverse effects seem possible with TMS. Because randomized trials often have relatively short followup, high quality observational studies can be good source for identifying longer-term adverse effects. Excluding these studies could miss important information on adverse events and should be noted as a limitation in the discussion. Reviewer 2: Page 6 – 2.1 The three questions posed regarding are certainly appropriate but would argue that effectiveness (versus efficacy) is a more relevant concept given the magnitude of the public health crisis and effectiveness of the treatment option are available. This is especially true when providing input to stakeholders directing care. When seeing a patient with one of these conditions, physicians must treat the patients based on the available treatment options and literature – not the literature that they would like to have available. Page 6 – 2.1 For safety questions especially, including large open or registry trials provides a much better estimate of the true harm than randomized controlled trials for multiple reasons besides just smaller numbers. There is the risk that the harm from the treatment can be overestimated as not accounting for "harm" due to sham which has many factors including illness progression, random events, unrelated events, etc. If the harm is incredibly low, however this becomes a non-issue and these types of studies can be very informative for the field and stakeholders. Page 6 – 2.1 For Cost questions – not clear why included comparisons with medication but excluded comparisons with other devices like ECT. For purposes of this review and given the intended audience, should only include studies involving U.S. cost structures as other health systems are so dramatically different.	We have added text to the limitations section 4.5 to address the concerns of Reviewer 1, and second concern of Reviewer 2. Regarding Reviewer 2 comment about effectiveness vs effiicacy, the topic selection document from the state of WA HCA stated high concerns for effiicacy and we focused the scope on this outcome versus effectiveness. Addressing comparative effectiveness was not feasible within the timeline allotted for this HTA. Regarding Reviewer 2 comment about cost questions, medications, ECT, or other standard therapies for treatment-resistant depression were eligible and this has been clarified in Table 2. However, cost-effectiveness studies with an ECT comparator were not identified in our search. Cost studies were restricted to U.S. based studies for exactly the reason the reviewer mentions.

Any additional comments about the Methods section?	Reviewer 1: The outcomes of clinical response, remission, and loss of diagnosis need to be defined. This is probably done best in the executive summary (maybe a small table) To help readers understand the logic, consider giving the rationale for critical methodological decisions. For example, why exclude comparative effectiveness studies? Reviewer 2: Many very positive aspects to the rigor and thoroughness in which this review was performed. Although a concerted effort is made to base the recommendations on data, there still is an element of judgement in the strength of evidence.	We have made revisions to section 2.3.3 to address the first comment from reveiwer 1. For the second comment, revisions have been made to section 2.3.2.For the comment of reviewer 2, we agree that some subjectiveity is inherent in SOE assessments; however, we provide detailed explanations in our SOE tables to offer readers transparency for our assessments.
Results		
Are there any studies you believe we may have missed?	Reviewer 1: No Reviewer 2: Given the parameters utilized for study selection, none known but again concerns about inclusion/exclusion mentioned above in order to address stated questions.	Comment appreciated.
Are there studies that you believe we should have excluded?	Reviewer 1: No, but I did not review individual studies in detail Reviewer 2: There are no specific studies to be excluded.	Thank you.
Do you believe we have inaccurately described any studies?	Reviewer 1: No Reviewer 2: Not that I could find.	Thank you.

Any additional comments about the Results?	Reviewer 1: Overall, the results are presented clearly but there are some inconsistencies in how data are reported and the clinical importance of "statistically significant" results is often unclear. Below are suggestions to consider: -In some instances, the "n" is reported but in most instances the "n" is not specified for a summary findings. Since readers will give more weight to findings from large studies, consider reporting the "n" for each major finding or for all eligible studies included for a specific condition (e.g. GAD, 2 RCTs, n=xx). Alternatively, n's are given in Table ES-1 and you could refer readers to this table earlier in the results presentation. -Studies of patients at any age were eligible. Most studies enrolled adults, but this doesn't come through clearly. For example, in ES 3.2 the final bullet states "no studies reported….findings for special populations…" but it would be clearer to state up front that the 2 RCTs enrolled adults (which I'm inferring based on the mean ages given in the full report). -Findings are sometimes given as pooled RR (95% CI) and these results are readily interpretable. Reporting the absolute risk difference (ARD) helps with interpretation (e.g., ES 3.3 bullet 1). I suggest that you consistently report the ARD. -In other instances, results are reported as "statistically significant" or "no significant difference." This type of reporting is more difficult to understand. We need to know if statistically significant differences are clinically important (e.g., ES 3.3, bullet 2) -ES 3.3, bullet 4: "…no significant difference by age" is unclear. What was the comparison (older adult vs younger adult, adult vs child, other)? -ES 3.3, bullet 4: In addition to the p value, can you give an effect size for the male vs female result? -ES 3.3, bullet 5: dTMS is reported as more effective (Y-BOCS reduction of 3.9), but again I'm uncertain if this is clinically meaningful. I need to know the minimum clinically important difference (MCID) to understand the cost-effectiveness. -ES 3.4: could the line "…which was estimated to fall within a minimum clinically important change for the most common measure…" be restated more simply as "…which was estimated to be clinically meaningful for the most common measure…"	All comments by reviewer 1 have been addressed with revisions in the specified sections. For comments by reviewer 2, we agree with the reviewer's suggestions and wherever possible have stratified the findings by TMS type. We included the number of sessions and timing of followup assessment on all forest plots. We did not identify any visual patterns with respect to these variables. Further, studies used slightly different thresholds for remission or response which explains some of the heterogeneity in findings. Most studies used a similar percent motor threshold so looking at variation by that characteristics was not feasible.

	-ES 3.4, bullet 4: consider giving the sample size for the special population studies. If they were large studies, then the finding of no difference would be more important than if from small studies. Reviewer 2: The combining of studies with different parameters (cTBS v. LfTMS) may provide misleading results as the treatments may or may not have fundamental differences – this is still not clear in the field. For syndromes that have reasonable number of studies – may be informative to look at minimal dose defined by number of treatments as well as percent motor threshold (especially for looking at age question)	
Discussion		
Do you think we missed any important points?	Reviewer 1: No, I think the narrative summary is on target. Reviewer 2: As mentioned above and is important for making recommendations for clinical practice guideline, randomized controlled trials are critically informative in determining the efficacy of a treatment, but other study designs can also be informative and sometimes more informative (especially safety, real-world effectiveness, and cost-effectiveness) than classic randomized trials. For some medical conditions, the literature is large enough to adequately address these questions with randomized trials, but others may require looking at other study designs to address these very important questions. Limiting the assessment of the literature to just randomized controlled trials does not provide a fair assessment of the effectiveness of a treatment. For example, if a large database demonstrates that hundreds of patients who previously failed many treatments for a devastating illness significantly improved with a treatment and there were no safety concerns, this would provide compelling effectiveness results. Obviously, there would be no specific support for efficacy of the treatment as could not determine if it was the specific treatment or some other aspect surrounding the treatment, but ultimately which is the most important in determining patient care.	To address the concerns of reviewer 2, we have added text regarding study design to the limitations section of the methods (2.3.5) and discussion (4.5).
Do you disagree with any of the discussion items?	Reviewer 1: No. Reviewer 2: I understand how the authors came to their conclusions but think – especially based on other types of available data - that the safety SOE of TMS in underrepresented.	We appreciate the reviewer's concerns and have included a paragraph in the summary of evidence and limitations section of the discussion about how across conditions, TMS is likely a low risk procedure.

Any additional comments about the Discussion?	Reviewer 1: The durability of treatment effects is addressed in the second paragraph on page ES-13. I think the durability is a critical outcome for clinical decision making and policy. However, durability is not addressed in any detail in the ES and the statement "The durability of TMS benefits was mixed among the handful of studies reporting at time points beyond the end of a course of treatment" (ES-13) left me wanting more. This statement helps me understand that the evidence is scant, but I want more. Can you give a little more detail to better address/contextualize this critical finding? Omitting Quality of Life outcomes is described as a limitation. I agree, but QOL typically tracks with symptom response/remission and thus may not be a critical limitation. I found Tables 25, 26, and 27 useful. Reviewer 2: Would consider mentioning data of effectiveness for comorbid conditions such as Anxiety with MDD, PTSD with MDD, etc, Clinical recommendations and availability of treatment should take into account multiple levels of evidence, severity of medical condition, and existing treatments with respect to effectiveness/safety.	We have added text to ES4.1 and Discussion Section 4.1 regarding durability of results to address the comments of Reviewer 1. Regarding Reviewer 2's comments, for practical reasons, we did not capture the impact on comorbid conditions unless there was a formal subgroup analysis. We included this as a limitation in the discussion (section 4.5).
Other Sections		
Any comments on the structured abstract, conclusion, figures, tables and appendices?	Reviewer 1: [pg ES-1] The sentence "evidence for the 1 study with cost outcomes was judged insufficient" is opaque. What was this study evaluating – cost effectiveness, cost-benefit, other? After reading the structured abstract, I made notes wanting more detail/greater clarity about who was studied (adults only?, illness severity, predominately patients with treatment resistant depression?), the dominate types of TMS studied and length of treatment/number of sessions, and whether TMS treatment was delivered as an "add-on" or monotherapy. Some of these issues are addressed in the longer executive summary, but I would urge you to add as much of this information as feasible to the abstract; it is needed context to interpret the results. Reviewer 2: I found these to be very informative and helpful. See above regarding conclusions.	We have made revisions to the abstract to address the comments of reviewer 1.
General Comments		

Is the report clearly written, adequately detailed and of an appropriate length?	Reviewer 1: Overall, the report is clearly written. I think most readers will focus on the executive summary and used the full technical report to get details on areas of greatest interest. The full report is too long for most readers, but the executive summary is a good length and contains appropriate detail (except where I've noted above) Reviewer 2: This report is very well written and has adequate detail and length for what was proposed.	Thank you.
Please make any additional comments you feel would help us improve the report.	Reviewer 1: No additional comments Reviewer 2: N/A	Thank you.

Public Comments and Responses

The Draft Evidence Report was posted for public comment from January 5, 2023, to February 6, 2023. One public comment was submitted. The names and affiliations of those submitting comments are summarized in ***Table 3.***

Table 3. Individuals or Organizations Submitting Public Comments on the Draft Evidence Report

Name	Title/Affiliation
Soo-Jeong Kim, MD and Carol Rockhill	Seattle Children's Autism Center; Washington State Council on Child and Adolescent Psychiatry(Council sign-on to previous comment from Dr. Kim)

Public comments and responses to comments are detailed in ***Table 4***. Complete copies of the comments submitted by individuals follow the table.

Table 4. Public Comments on Draft Evidence Report and Specific Responses

Public Comment	Response
Dear Health Technology Assessment Program Committee, We, as child adolescent psychiatrists, would like to request your support for transcranial magnetic stimulation (TMS) therapy for youth. TMS has excellent safety data in youth similar to the data around adult safety and has been investigated for various psychiatric disorders including among others major depression, obsessive compulsive disorder (OCD), and autism spectrum disorder. Currently TMS is only available to individuals and families privileged enough to afford to pay for it out-of-pocket. This leaves lower-income families, disproportionately represented by black, indigenous, and people of color (BIPOC) individuals, without access to an important therapy. Coverage of TMS therapy for youth is an equity issue. Among these serious conditions, treatment resistant depression is extremely concerning as it has a significant impact on individuals, families as well as on	The study selection criteria we used did not limit the populations considered. We identified only 1 eligible study in adolescents and no eligible studies in children. (Section 3.4.2 "Special Populations")

society as a whole. Suicidal ideation and suicide attempts are often associated with depression, and suicide is the second leading cause of death in adolescents. In 2019, more than 40% of behavioral health related Emergency Department (ED) visits at Seattle Children's Hospital were related to suicidal behaviors, mostly in the context of depression. While pharmacologic interventions are available for these conditions, not everyone responds to medication well. According to the large studies funded by the National Institute of Mental Health (NIMH), such as The Treatment for Adolescents with Depression Study (TADS) and Treatment of Resistant Depression in Adolescents (TORDIA), a third of teens with depression did not respond to treatment, and the likelihood of remission after two failed antidepressant trials appears to be roughly 10% per medication. The financial cost of untreated depression is monumental; it is a leading cause for ED visits and hospitalizations. Compared to the direct and indirect cost of untreated depression in patients, families, and society, the cost of a TMS course is relatively low especially considering the risk of suicide associated with treatment resistant depression. Based on positive data from adults as well as positive reports from case series in children, we believe TMS therapy should be considered as a beneficial non-pharmacologic option for multiple psychiatric conditions. TMS is currently accessible to families who are able to pay out-of-pocket, leaving behind the majority of children without alternative treatment options when first-line treatments are not successful. Having TMS available for these conditions might help alleviate the financial strain and burden on emergency departments, and costly inpatient hospitalization. It would also address inequities in providing access to safe and efficacious treatment, and alleviate suffering to a greater proportion of children and adolescents in our communities.	