Washington State Health Care Authority

Health Technology Assessment

Nonpharmacologic Treatments for Treatment-resistant Depression

Response to Comments on Draft Report

February 21, 2014

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Nonpharmacologic Treatments for Treatment-Resistant Depression

Response to Public Comments on Draft Report

February 21, 2014

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Response to Public Comments, Draft Report

Nonpharmacologic Treatments for Treatment-Resistant Depression

Hayes, Inc. is an independent vendor contracted to produce evidence assessment reports for the WA HTA program. For transparency, all comments received during the comments process are included in this response document.

Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only. When comments cite evidence, the information is forwarded to the vendor for consideration in the evidence report.

This document responds to comments from the following parties:

- Two parents of an adult child who has had treatment-resistant depression (TRD)
- David H. Avery, MD, Professor Emeritus, University of Washington School of Medicine, Psychiatric Medicine Associates

Table 1 provides a summary of comments with responses.

Table 1. Public Comments on Draft Report, Nonpharmacologic Treatments for Treatment-Resistant Depression

Key: AD, antidepressant (medication); AHRQ, Agency for Healthcare Research and Quality; CI, confidence interval; ECT, electroconvulsive therapy; RCT, randomized controlled trial; rTMS, repetitive transcranial stimulation; TRD, treatment-resistant depression

Comment and Source	Response
Comments on Draft Key Questions	
January 16 e-mail from 2 parents of young adult with TRD	
The commenters reported that their child is in remission due to TMS after 4 years of TRD during adolescence and no benefit from medication and talk therapy.	Thank you for your comments. No changes are needed in the report.
The commenters quoted a Premera Blue Cross policy: "ECT continues to be the most effective treatment for treatment-resistant depression, but the high incidence of functionally-impairing adverse cognitive effects renders ECT undesirable in many cases. In addition, there is a cohort of patients who have failed or cannot tolerate antidepressant medications and ECT. For those patients, … TMS is the only treatment option that remains, and that stands between possible relief of depression and continued indefinite suffering."	
"Furthermore, any health plan that imposes treatment limitations on mental health benefits that are more restrictive than those imposed on medical/surgical benefits is vulnerable to challenge under both federal and state mental health parity rules. Administrative and legal challenges alleging mental health parity violations are growing and will continue to grow until health plans provide mental health parity. We have been studying the TMS policies of the health plans that serve Washington residents. Aetna, Group Health and Regence, all cited in your report, apply standards to exclude TMS that are more restrictive than and/or are applied more stringently than the standards they use	

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to cover corresponding medical/surgical benefits. Such action violates the mental health parity rules and will be challenged. Also, the three referenced plans all provide just one intensive outpatient mental health treatment for patients with treatment resistant major depression (ECT) while providing a wide scope of intensive outpatient treatments for patients with medical/surgical conditions. Again, such action violates the mental health parity rules and will be challenged. There are two health plans serving Washington residents that currently cover TMS - Premera Blue Cross and Health Net. As administrative and legal challenges succeed, more will follow. Please consider both the medical and legal reasons supporting coverage for TMS as you finalize HCA's guidance regarding nonpharmacologic therapies for treatment resistant major depression. Thank you!"	
January 21 Letter from David Avery, MD	
"The emphasis on more rigorous research methodology is appropriate for developing suggestions for future research in this area. However, the approach is lacking in helping determine what the most appropriate treatment is for current patients. The strict inclusion criteria exclude many very good research studies that were done well before the inclusion criteria were developed. These older studies have informed both patients and clinicians in their search for the most appropriate treatment."	Thank you for your comment. See responses to specific examples of this type of omission.
"For example, the systematic assessment of the degree of medication resistance first started in the 1990's; most of the ECT studies were done prior to that time. These ECT studies were excluded from the HTA analysis even though most clinicians and researcher acknowledge	Thank you for pointing out the uncertainty involved in selecting ECT studies for a report on treatment-resistant depression. The AHRQ report's approach to studies where medication resistance was uncertain was observed in the WA HTA report. All of the RCTs of ECT that were

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Comments on Draft Key Questions	
that many if not most of these patients in these studies were treatment resistant. Even in the AHRQ report (Gaynes, 2011) 'Tier 3' was created to recognize this issue: 'Tier 3 Evidence: studies in which the number of prior failed treatments was not **specified but the clinical situation suggested a high probability of patients having two or more prior antidepressant treatment failures**; these data have probable relevance to TRD. Studies that did not specify the number of failed treatments but noted that all subjects were referred for ECT were included in this tier.'"	included in the AHRQ report, 2 of which were in "Tier 3," were reviewed in detail. No RCTs designed to test the effectiveness of ECT were identified in the literature published since the AHRQ report, so no RCTs of ECT were excluded on the basis of a lack of explicit data about prior AD treatment.
"Many studies have compared antidepressant medications with ECT. Some of these studies were summarized in a meta-analysis by the UK ECT Group (2003) and found a clear superiority for ECT over antidepressant medication. (See figure.) Even though some other meta-analyses from the UK ECT Group study were cited in the HTA report, this meta-analysis was excluded." (The commenter provided the forest plot from this meta-analysis. There was an effect size of –0.802 [CI, –1.290 to –0.289], favoring ECT, according to the random effects model.)	Thank you for calling attention to this evidence. The 2011 AHRQ evidence review was chosen as the most recent systematic review of ECT and rTMS in patients with TRD and was used as a guide to selection of other evidence. The meta-analysis of ECT versus simulation (sham) was felt to be of uncertain applicability to the topic and limited generalizability to current practice. Nine of the included studies were excluded by the AHRQ review because of publication prior to 1980. The authors of the AHRQ report note that even the 2 sham-controlled studies that *were* included in their report were published in the early 1980s, "limiting comparability to other studies in this report due to difference in antidepressant availability and study populations (e.g., no documented antidepressant failures)" (p. 39). Another 3 studies included in this particular meta-analysis by the UK ECT Group were excluded from the AHRQ report because of "wrong population," which implies that the AHRQ authors did not judge the clinical situation to suggest a high probability of having ≥2 prior AD failures. Other meta-analyses reported in the UK review (unilateral versus bilateral ECT, high dose versus low dose, and frequency of scheduling) were cited in spite of uncertain applicability to TRD and generally very old publication dates because no other evidence on these topics was

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	available.
"In addition, comparing response and remission rates across studies provides useful data. On page 34 of the HTA report the analyses of medications in treating TRD depression are summarized. (There was one important typo in Table 6. 'Remission' and 'Response' are mistakenly transposed.)" The commenter refers to a point made in the HTA report that data on remission rates in the pharmacotherapy arms of 12 trials (analyzed in the AHRQ review and summarized in Table 6 of the HTA report) "'provide an estimate of the degree of improvement that might be expected from new pharmacologic therapy and from no change in treatment as a response to TRD.'" The commenter adds "However, the magnitude of improvement is never used as an anchor compared with ECT studies. ECT studies show better response rates and remission rates compared to those seen in medication studies. If one compares the data from the AHRQ summary of medication effects in TRD with studies of ECT, the remission rates are clearly higher compared to having the patient continue on the same antidepressant that is not working, compared to switching to a new antidepressant, and compared with augmentation. (See figure.) Comparing across studies is not optimal, but the comparison is consistent with other studies in which patients were randomized to either ECT or medication. These data continue to be very relevant to the clinical situation. The most important issue is 'what is the likelihood of response or remission with ECT compared to the likelihood of response with yet another trial of an antidepressant medication?' The magnitude of the response to ECT is greater than with pharmacologic treatment."	Thank you for catching the error in Table 6 (Table 7 in the Final Report); it has been corrected. Thank you for pointing out that the within-group data on pharmacotherapy for TRD had not been compared with the ECT studies. Since the RCTs of ECT did not report remission rates, remission rates reported in a meta-analysis of uncontrolled studies have been added to the discussion of ECT findings.
'The UK ECT study also found clear superiority of ECT over simulated ECT. (See figure.) Even though some other meta analyses from the UK ECT Group study were cited in the HTA report, this meta-analysis from	This particular meta-analysis by the UK ECT Group was excluded as evidence for #1a for reasons similar to those for which the meta-analysis of ECT versus pharmacotherapy was excluded: most of the studies were

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the UK ECT Group study were cited in the HTA report, this meta-analysis was excluded. Note that the mean effect size for ECT in the ECT-Simulated ECT studies of 0.91 is much greater than for antidepressant medications, which are usually about 0.39-0.49 (Khan, 2007, Berman, 2007). The HTA report notes the lack of ECT-simulated ECT controlled studies for patients who fulfill their strict criteria for TRD. Such a study would be unlikely approved by a human subjects committee. TRD patients have a high suicide rate and low placebo response rate. It would probably be considered unethical to administer simulated ECT to such a population of ill patients. In addition, there are already data indicating that ECT is superior to sham stimulation in populations that contains a high proportion of TRD patients." The commenter provided the forest plot from this meta-analysis. There were significant effect sizes of –0.911 and –0.908 according to fixed and random effects models.]	published prior to 1980. One study was excluded by the AHRQ report because of poor quality. Two studies (Johnstone et al., 1980; West et al., 1981) are reviewed in both the AHRQ and WA HTA reports. Regarding the comparison of results for ECT and pharmacotherapy from different sets of studies, we felt that the pooled estimates reported by Heijnen et al. (2010) for ECT and the AHRQ review (Gaynes et al., 2011) for pharmacotherapy were more germane to the topic since both are directly applicable to patients with medication resistance. However, the UK ECT Group results for ECT versus sham and versus pharmacotherapy, along with other references supplied by the commenter for effect sizes based on AD medication trials, have been added to the discussion of *Magnitude of Benefit* in the ECT **Findings** section of the **EVIDENCE SUMMARY**. Thank you for your comment about the ethics of administering simulated (sham) ECT to patients with TRD. This is an important consideration in policy deliberations but does not affect an assessment of the available evidence. Statements have been added to the **Overall Summary and Discussion** and **Limitations of this Report** sections to clarify that a large body of older evidence concerning ECT was not represented. In addition, the results of the UK ECT Group's meta-analyses of ECT versus simulation (sham) and ECT versus pharmacotherapy have been cited in the discussion of evidence for Key Question #1a to help provide greater context.
"The debate over the definition of TRD is also complicated by medication intolerance. Many patients are simply unable to tolerate antidepressant medication and are unable to achieve an adequate dose of antidepressant medication. These medication failures do not count toward medication-resistance in the HTA definition. To the patient and clinician, it is a moot point whether the dose and duration	Thank you for pointing out this important clinical consideration. The WA HTA report does not endorse a definition of TRD but cites definitions from various sources. The **Gaps in the Evidence** list includes a call for a standard definition of TRD, and this item has been amended to include a recommendation of "acknowledgement that AD failure can be due to intolerable side effects" (This point is made elsewhere in the report in

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were adequate. If the patient was intolerant to the medication, the medication failed."	descriptions of various definitions of an 'adequate prior trial').
"The HTA report has applied a rigorous approach that helps guide future research, but the report excludes important clinical data that is very relevant to the current clinical situation."	Thank for your insights. The HTA report reviews the available published evidence that meets specified inclusion criteria, with consideration of clinical context. However, HTA methodology is not designed to address all clinical considerations that are not covered within the body of evidence.

Dear Ms. Masters:

Thank you for the opportunity to review the Washington State Health Care Authority Health Technology Assessment for Non-pharmacological Treatments for Treatment-Resistant Depression.

The emphasis on more rigorous research methodology is appropriate for developing suggestions for future research in this area. However, the approach is lacking in helping determine what the most appropriate treatment is for current patients. The strict inclusion criteria exclude many very good research studies that were done well before the inclusion criteria were developed. These older studies have informed both patients and clinicians in their search for the most appropriate treatment.

For example, the systematic assessment of the degree of medication resistance first started in the 1990's; most of the ECT studies were done prior to that time. These ECT studies were excluded from the HTA analysis even though most clinicians and researcher acknowledge that many if not most of these patients in these studies were treatment resistant. Even in the AHRQ report (Gaynes, 2011) "Tier 3" was created to recognize this issue: "Tier 3 Evidence: studies in which the number of prior failed treatments was not specified **but the clinical situation suggested a high probability of patients having two or more prior antidepressant treatment failures**; these data have probable relevance to TRD. Studies that did not specify the number of failed treatments but noted that all subjects were referred for ECT were included in this tier."

ECT vs Pharmacotherapy

Many studies have compared antidepressant medications with ECT. Some of these studies were summarized in a meta-analysis by the UK ECT Group (2003) and found a clear superiority for ECT over antidepressant medication. (See figure.) Even though some other meta-analyses from the UK ECT Group study were cited in the HTA report, this meta-analysis was excluded.

ECT vs Pharmacotherapy (UK Review Group, 2003)

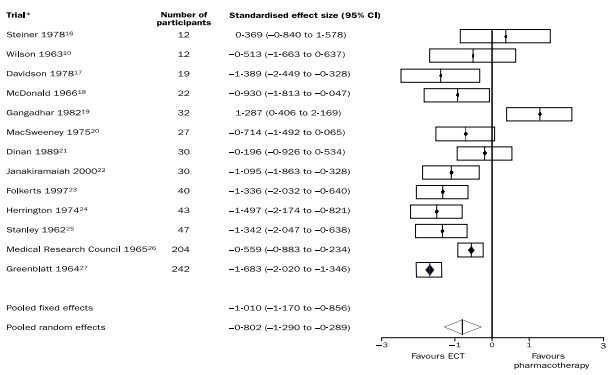
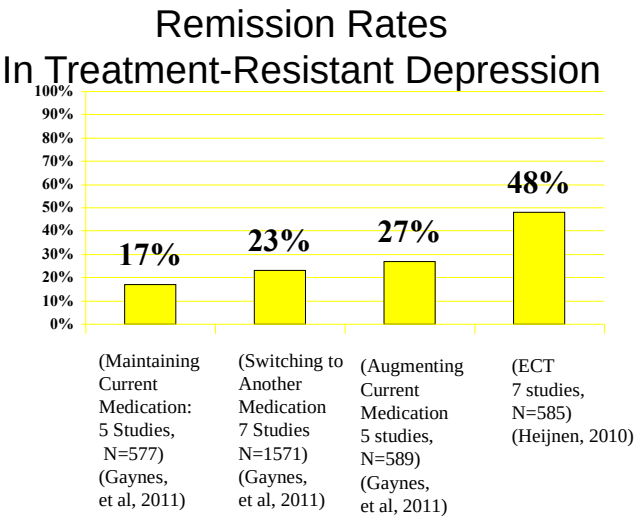


Figure 3: **Effect of ECT versus pharmacotherapy on depressive symptoms**
*Other trials not included: Kendrick 1965,[28] Bruce 1960,[29] Bagadia 1981,[30] Hutchinson 1963,[31] Robin 1962.[32]

In addition, comparing response and remission rates across studies provides useful data. On page 34 of the HTA report the analyses of medications in treating TRD depression are summarized. (There was one important typo in

Table 6. "Remission" and "Response" are mistakenly transposed.) “These within-group findings provide an estimate of the degree of improvement that might be expected from new pharmacologic therapy and from no change in treatment as a response to TRD. As noted by Gaynes and colleagues, **the estimates provide an anchor against which to judge the magnitude of improvement in patients undergoing nonpharmacologic treatment for TRD** (Gaynes et al., 2011).” However, the magnitude of improvement is never used as an anchor compared with ECT studies. ECT studies show better response rates and remission rates compared to those seen in medication studies. If one compares the data from the AHRQ summary of medication effects in TRD with studies of ECT, the remission rates are clearly higher compared to having the patient continue on the same antidepressant that is not working, compared to switching to a new antidepressant, and compared with augmentation. (See figure.) Comparing across studies is not optimal, but the comparison is consistent with other studies in which patients were randomized to either ECT or medication.



These data continue to be very relevant to the clinical situation. The most important issue is “what is the likelihood of response or remission with ECT compared to the likelihood of response with yet another trial of an antidepressant medication?” The magnitude of the response to ECT is greater than with pharmacologic treatment.

ECT vs Simulated ECT

The UK ECT study also found clear superiority of ECT over simulated ECT. (See figure.) Even though some other meta-analyses from the UK ECT Group study were cited in the HTA report, this meta-analyses were excluded. Note that the mean effect size for ECT in the ECT-Simulated ECT studies of 0.91 is much greater than for antidepressant medications, which are usually

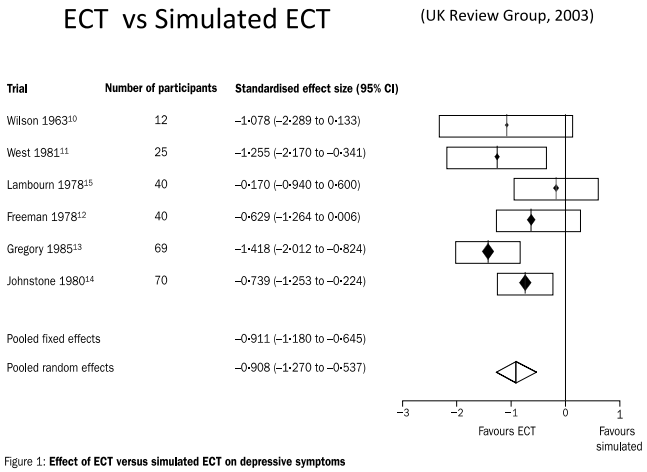


Figure 1: **Effect of ECT versus simulated ECT on depressive symptoms**

about 0.39-0.49 (Khan, 2007, Berman, 2007). The HTA report notes the lack of ECT-simulated ECT controlled studies for patients who fulfill their strict criteria for TRD. Such a study would be unlikely approved by a human subjects committee. TRD patients have a high suicide rate and low placebo response rate. It would probably be considered unethical to administer simulated ECT to such a population of ill patients. In addition, there are already data indicating that ECT is superior to sham stimulation in populations that contains a high proportion of TRD patients.

The debate over the definition of TRD is also complicated by medication intolerance. Many patients are simply unable to tolerate antidepressant medication and are unable to achieve an adequate dose of antidepressant medication. These medication failures do not count toward medication-resistance in the HTA definition. To the patient and clinician, it is a moot point whether the dose and duration were adequate. If the patient was intolerant to the medication, the medication failed.

The HTA report has applied a rigorous approach that helps guide future research, but the report excludes important clinical data that is very relevant to the current clinical situation.

Sincerely,

David Avery, M.D.
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