Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults*

Draft review available for public comment from November 08, 2010 to December 06, 2010.

Research Review Citation: Gaynes BN, Lux L, Lloyd S, Hansen RA, Gartlehner G, Thieda P, Jonas D, Brode S, Swinson Evans T, Crotty K, Viswanathan M, Lohr KN. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Review No. 33. (Prepared by RTI-UNC under Contract No. 290-02-0016I.) AHRQ Publication No. 11-EHC056-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1	Executive Summary	ECT should be utilized as a very last resource for nonpharmacologic interventions for treatments due to the long term side effects of memory loss etc. I am amazed that this form of treatment is still being used as a viable option for treatment of depression.	Our review addressed a topic and suggested interventions that arose through an open process involving the public, the Scientific Resource Center for AHRQ, and various stakeholder groups. The use of ECT was an issue submitted by the nominator of the topic.
Peer Reviewer #1	Executive Summary	No comment	
Peer Reviewer #2	Executive Summary	Perusing Table ES-1, it is hard to see that there are many points of substantive divergence when Tier 1 alone is compared against Tiers 1-3. While I appreciated the very significant amount of work underlying the differentiation into Tiers 1-3 and MMD alone or mixed groups, I struggled to find a compelling description of why this was deemed necessary (the most convincing argument would be that different patterns of results were apparent dependent on the definitions of the population employed). It was probably important to examine this question in a systematic way, but perhaps there is a way to present the data that is not quite so daunting to the reader.	We agree. We have changed the strength of evidence tables and text in the Discussion and the Executive Summary tables to only include Tier 1 studies.
Peer Reviewer #4	Executive Summary	In the summary table (included in the executive summary and discussion sections) it could be informative to describe sample sizes or give some other indicator of precision. This would be especially useful for interpreting findings of no difference (either treatment A is not superior to sham/placebo OR treatment A does not differ significantly from treatment B). This information is provided in the main report, but some (if only brief) indicator of precision would be useful in the executive summary.	We agree, and we have added a sample size column to these summary tables.
Peer Reviewer #1	Introduction	The introduction provides a cogent rationale for the detailed analyses. The authors state the importance of non-pharmacologic interventions for treatment resistant depression, their growing use beyond ECT, and the need to have some evidence-based comparison for ECT, VNS, rTMS and CBT/IPT with either usual care or pharmacotherapy	Thank you.
Peer Reviewer #2	Introduction	The tables were extremely helpful and laid out many aspects of the approach and rationale in an efficient and effective manner.	Thank you.
Peer Reviewer #3	Introduction	The introduction is thoughtful and appropriate.	Thank you.

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Peer Reviewer #4	Introduction	To put this question in context, it might be helpful to point out that most depression “treatment failure” in community practice results from low-intensity treatment or non-adherence – rather than from true treatment “resistance”.	This point has been addressed in the introduction, following figure 2.
Peer Reviewer #5	Introduction	This is excellent in setting the context for the problem and its importance. It gives a nice overview that orients that orients the reader to the central issues involved in the area.	Thank you.
Peer Reviewer #7	Introduction	This CE review summarizes the CE data on the efficacy, effectiveness, and harms of ECT, rTMS, VNS and CBT?IPT in patients with treatment-resistant depression (TRD).	Thank you.
Peer Reviewer #9	Introduction	The introduction is clear and provides a good overview of the problem, the treatments covered, and the impetus for the speciifc questions covered in the report. As each treatment is reviewed in the introduction, this reviewer wondered if the evidence base for the statements cited are of the same quality as those in the results.	The evidence cited in the Introduction has not been systematically reviewed nor has its quality been formally assessed, so it is difficult to determine whether the evidence is of equivalent quality relative to the evidence base in the Results section.
Peer Reviewer #11	Introduction	For the most part the introduction is quite good. On page 23, line 13, the statement "rTMS reportedly does not have the seizure or cognitive risks of ECT" is misleading. rTMS has a risk of seizure and this should be clearly stated.	This correction has been made.
Mark Demitrack, Neuronetics	Introduction	Page 22-23: There is no medical or scientific reason to indicate that TMS should be restricted in use for patients who have metal “anywhere in the body”. The magnetic field produced by the magnetic coil in a TMS procedure is spatially confined to a small volume near the coil surface. Current product labeling only restricts TMS use in patients who have magnetically active metal that is non-removable and is located within 30 cms of the face of the treatment coil. This restriction also does not apply to the presence of dental hardware in the mouth, which is permissible.	We have corrected this misstatement in the Introduction.
Jean Anderson, Ph.D.	Methods	Equating of CBT & IPT confounds results. Both CBT & IPT are non-equivalent with impersonal (all other) modalities not just in time involved but in essential human content. The WHO of both CBT & IPT modes is definitive and cannot be generalized. Better to compare all non-personal modalities, then separately, various detailed forms of personal intervention.	The question of whether the effects of CBT and IPT can potentially be quantitatively combined or presented as separate results is a reasonable one, However, given that no eligible IPT studies were identified, the concern does not affect the results in this report.
Peer Reviewer #1	Methods	The authors conducted an exhaustive literature review, winnowing down the number to about 48 papers with justifiable inclusion and exclusion criteria. They explicitly state and describe the search strategies, which are logical. The full domains of diagnostic criteria and outcome measures are appropriate. The authors rightly state that the long-standing lack of a standard definition of treatment resistant	Thank you.

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		depression hampers any effort to compare treatments. All of the statistical methods used to compare the limited number of studies are appropriate.	
Peer Reviewer #2	Methods	the a priori justification for the Tiering approach is relatively weak. I found the justification for the need to differentiate Tier II and III to be particularly lacking. I found it hard to follow from a PICOT perspective. Particularly difficult to determine timelines, which for some nonpharmacological treatments may be a significant issue. In this instance timelines of harms is also not a trivial issue. It seemed clear that the comparator groups represented an issue in some studies but then it was hard to determine how this was factored into the overall assessments. . . It was difficult to determine whether the division of studies into Tiers 1, 2 and 3 resulted in a substantial difference to the pattern of results or the conclusions drawn. Were there a priori reasons for this distinction into the three tiers?	We have clarified our rationale in the Methods section (under "Treatment Resistant Depression and Tier Classification System". We appreciate the query of whether considering Tiers 2 and 3 added value to the results. The reasons to distinguish into three tiers resulted from a limitation of the evidence base identified in our initial literature reviews—only a very small proportion of the eligible literature sufficiently clarified that the enrolled populations had 2 or more prior treatment failures or stratified their analyses by the whether the patient had 1 vs. 2 or more prior treatment failures (our working definition of TRD). Given the evolving concept of TRD (noted in our text), this absence is not surprising. However, exclusion of studies that used 1 or more treatment failures for eligibility did not seem to reflect the evidence base for TRD, as many patients in these studies did have 2 or more treatment failures. Similarly, many studies that refer to treatment resistant patients and likely have patients who have failed multiple prior treatments (e.g., ECT studies) fail to describe the number of prior treatment failures in the study, or fail to clarify whether the prior treatments have been adequate, or involve some patient with no treatment failures but fail to stratify their analyses by whether patients had prior treatment failures. Not considering these studies, some of which are the highest quality in the field, would also not accurately reflect the available data. Accordingly, while we focus on Tier 1 (TRD) studies, we also acknowledge the other relevant studies.

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Peer Reviewer #3	Methods	The inclusion and exclusion criteria are justifiable and the search strategies explicitly stated and logical. The review was well conducted.	Thank you.
Peer Reviewer #4	Methods	The inclusion of narrower and broader definitions of TRD is appropriate and clearly described	Thank you.
Peer Reviewer #5	Methods	The inclusion criteria are generally justifiable	Thank you.
Peer Reviewer #5	Methods	It was not completely clear to me why the authors had included studies involving bipolar patients. It is true that mood disorders can be considered across a spectrum from unipolar to bipolar and that may be what motivated the reviewers. On the other hand, it might have been cleaner to limit the findings to unipolar or explain more clearly why they included the bipolar group.	We appreciate the reviewer's comment and agree that preferably the selection criteria would be limited to MDD patients only. However, our initial literature review indicated that were we to exclude studies that exclusively had MDD patients (and no Bipolar patients), the identified literature would be dramatically small. In consultation with our TEP members, we attempted to identify a % of Bipolar patients that would be unlikely to substantially distort results for the remaning MDD population. After discussion with our TEP, we agreed on a threshold of 20% (e.g., in a study of 50 patients, no more than 8 could have Bipolar Disorder). We believe this rational is clearly described in the Introduction at the end of the "Patient Populations Included" section. Also, we have acknowledged this mixture as a limitation of the evidence base. No new text has been added.
Peer Reviewer #5	Methods	The authors use of search strategies seem excellent as do their outcome measures of remission, response, depression severity and quality of life/functional measures.	Thank you.
Peer Reviewer #7	Methods	The inclusion and exclusion criteria are justifiable and the TRD population data are tiered based on 3 different definitions of TRD. The search strategies are explicitly stated and are logical. The definitions & diagnostic criteria for the outcome measures are appropriate. The statistical methods used are appropriate.	Thank you.
Peer Reviewer #9	Methods	Methods are well conceived and executed. Figure 3 is extremely helpful. The definition used for TRD is sound and the use of tiered evidence based on how explicitly studies conformed to this definition is very helpful. Inclusion of tiers 2-3 helpful as they probably represent what is most typically encountered in clinical practice. Only	Thank you.

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		studies considered good or fair based on AHRQ's grading system were included which is appropriate. The authors completed an exhaustive review of studies.	
Peer Reviewer #9	Methods	Head to head comparisons for these treatments, as for most treatments, are animals rarely found in nature as the sample size needed for such trials is basically prohibitive, given our current statistical methods. Therefore it is good that this report includes trials comparing to controls, sham therapies and pharmacological options.	Thank you.
Peer Reviewer #11	Methods	The methods were clearly presented and appropriate.	Thank you.
Peer Reviewer #1	Results	The comprehensive results present an appropriate level of detail and the characteristics of the studies are clearly described. The key messages, that the field is in its infancy and our ability to compare these treatments is limited as a result, are explicit and applicable. Figures, tables, and appendices are clear, adequate, and descriptive. No studies were overlooked or included that should have been excluded to the best of my knowledge.	Thank you.
Peer Reviewer #2	Results	Was there a reason to believe that having a relatively small portion of the sample meet criteria for bipolar was reason enough to isolate those studies? More importantly, perhaps, was there convincing evidence in the MDD alone group that no portion of the sample might have had bipolar disorder, to that date unrecognized? It was particularly difficult to know whether the distinction between Tiers 2 and 3 (which appear to be reliably combined) resulted in useful additional information. The results are complex to follow (there is a lot of data) and unless there are some key take-away messages about how the various definitions of TRD systematically influence the extant data, it is not clear that it adds enough value to make it worth the additional work for the reader.	On average, consideration of the additional two tiers supported the findings in Tier 1. We selected a 20% cut-off because we hypothesized that such a threshold would involve a small enough number of bipolar patients to not affect the outcome, but we did not know for sure whether this threshold was reasonable. Our analyses, though limited to a small number of studies, did not suggest a substantial difference between MDD-only and mixed populations. We have revised the report to address only Tier 1studies in the Strength of Evidence tables in the Results section, in the Discussion section, and in the Executive Summary. The detailed analyses of Tiers 2 and 3 are still in the Results section, but they are not addressed in the Discussion or Executive Summary to make our conclusions about the available evidence for TRD clearer.
Peer Reviewer #2	Results	I struggled to understand what was the value of the analysis of the pharmacological studies? I understood the logic in the approach but it was difficult to appreciate how the results of this section were then	The rationale for including these analyses is presented in the Introduction: "For many patients with TRD, the

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		used to make some useful statement of relevance to nonpharmacological treatments. This section did not seem to figure prominently in the lead in to the report nor in the conclusions from the report. And of course, the pharmacological analysis is not expected in a report that identifies itself as focused on "nonpharmacological" treatments. If the pharmacological data are really critical for an understanding of the overall pattern of results, should they not be reflected in the title?	consideration of another pharmacologic intervention (whether a single agent or combination) remains the next decision step. To place the comparative effectiveness of nonpharmacologic treatments within the context of pharmacologic considerations, we also consider clinical outcomes for a next step pharmacologic treatment based on augmentation and combination mediations commonly used in clinical practice." In the Discussion of KQ 1b, we note: "We attempted to determine mean changes in depressive severity, relative risks of response, and relative risks of remission for pharmacologic vs. control studies to allow a comparison with similar outcomes in the nonpharmacologic vs. control trials (KQ 1a, indirect). However, there were no comparable, common control groups not receiving a mood-related medication to allow such comparisons. Instead, we determined mean average outcomes for pharmacologic treatments. . . While these results provide an idea of the general degree of response seen with next-step pharmacologic treatment in TRD, they serve as an uncontrolled case series and should only be compared to nonpharmacologic outcomes with caution." We had hoped that, through indirect comparisons, we could compare results from a next step pharmacologic treatment to those from a next step non-pharmacologic treatment. Unfortunately, the studies did not allow such a comparison, so we provided a generally average of what a next step pharmacologic treatment might provide to allow the reader to have some kind of comparison to results from a next step nonpharmacologic intervention. As noted in the Discussion, any comparison with these

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			data must be made with caution.
Peer Reviewer #3	Results	The results are presented in a clear and thorough manner.	Thank you.
Peer Reviewer #4	Results	Use of a log scale on a narrow graph in figures summarizing dichotomous outcomes (e.g. fig 6, fig 7) makes them very difficult to interpret. If a log scale is to be used, then the figure should be expanded much wider and the citation information reduced in size.	We appreciate the comment about ease of reading. However, we are bound by the limitations of the software program that we have used. We believe that it is important to retain the upper and lower limits, so we will keep the graphs as they are.
Peer Reviewer #5	Results	The tables are the best part of results in that it allows the reader to quickly view the data. The text itself becomes rather redundant reading over the entire work, but I doubt many readers will do so.	We appreciate the comment, but we feel the text is necessary to adequately clarify the findings. We have, however, substantially reduced the size of the Results section by limiting Strength of Evidence findings to Tier 1, which should make reading the Results section easier.
Peer Reviewer #5	Results	It is not clear to me why some interventions were excluded or not even mentioned. For example, there is considerable evidence that deep brain stimulation of different areas (e.g. BA 25) has substantial efficacy in experimental studies, yet this is not described. This is an important area of research with significant impact on our understanding of depression circuitry. Similarly, mindfulness-based cognitive therapy has been utilized both for relapse prevention, but also for treatment resistant depression in several open trials with RCTs underway yet this is not even mentioned (although Kenny's study is referenced).	We had already identified in the Discussion section in Future Research Needs that including newer nonpharmacologic treatments (including deep brain stimulation) will be important. We have added a reference to recent mindfulness based trials that are currently underway. Kenny MA, Williams JMG. Treatment-resistant depressed patients show a good response to mindfulness-based cognitive therapy. Behav Res Ther 2007; 45: 617-625
Peer Reviewer #6	Results	Comment based on my clinical experience in treating individuals wtih TRD. There are a fair # of patients who I would not diagnose as having a bipolar spectrum disorder, but who have adverse effects to traditional antidepressants with hyperarousal, irritability, insomnia, mood lability, anxiety or other features that might otherwise suggest bipolar spectrum. If this is reflected in the papers, it may deserve a comment. In other words, the 20% bipolar mix, rather than representing pesky interference could be due to some of these patients who we don't know exactly how to classify but we often end up treating with some form of mood stabilizer.	We agree that this is a key clinical point; however, the available research data base does not allow us to address this question.

Peer Reviewer #7	Results	The amount of detail presented in the results section is complete and appropriate. The characteristics of the studies are clearly described and key messages are stated explicitly and are applicable.	Thank you.
Peer Reviewer #7	Results	All figures, tables and appendices are adequate and descriptive. The investigators did not overlook any studies that ought to have been included nor did they include studies that ought not to have been excluded.	Thank you.
Peer Reviewer #9	Results	It appears that the literature reported is comprehensive and the authors have done an excellent job in summarizing the data in as clear a format as is possible (tables plus qualitative summaries and detailed analyses) given the overall complexity and heterogeneity of the studies reviewed.	Thank you.
Peer Reviewer #11	Results	It is not clear to me why studies contrasting different types of ECT were not included. All forms of ECT are not equally effective. This is both a significant omission and over simplification of the issue, which may lead to spurious conclusions. This is important since ECT is far and away the most effective treatment for TRD. Otherwise, the results are quite comprehensive and presented clearly. This will be a useful reference for the field.	We agree that all forms of ECT were not effective and that the identifying the most effective form of ECT is a complicated issue. However, an assessment of the varying forms of ECT was not a part of the scope of this review comparing nonpharmacologic treatments for TRD. Further, consideration of the different forms of ECT would not affect our findings, given the few eligible studies identified.
Mark Demitrack, Neuronetics	Results	Page 136: It appears that Table 79 should match the information reported in Table 68 earlier in the text.	This has been corrected.
Bernard H. Berne	Key Question 1	The results section states in Table ES-1 that the strength of evidence for the effectiveness of repetitive transcranial magnetic stimulation (rTMS) vs. sham for all tiers is either high or moderate for response rate and remission rate. This is not correct. None of the cited investigations utilized a real "sham" treatment that created the localized sensations (including scalp and neck twitching, tingling and pain) that active rTMS frequently produces. These sensations confound study blinding. Subjects that experience such sensations (because they are receiving active rTMS) are likely to conclude that they are receiving active treatment and thus may experience a high "placebo response" that appears to show effectiveness of treatment. Subjects receiving sham treatment do not experience such sensations, have a lower "placebo response", and show less effectiveness of treatment. Therefore, the apparent moderate to high "strength of effectiveness" of active vs. sham rTMS may be due to placebo effects, rather than to actual treatment effects. Considering this, the "strength of effectivess" for rTMS vs. sham comparisons for	We have now noted in the section on Limitations in the Evidence Base the challenge of finding an adequate sham control group for rTMS (as well as the other non-pharmacologic interventions). With our updated literature search, we have now included the George, et al, 2010 in the report as a Tier 2 study. We note that the findings from the George et al study are equivalent to results from our quantitative syntheses of Tier 1 and Tier 2 studies. Also, the observation that the overall number of remitters was “less than one would like” is an opinion rather than a conclusion based on facts. Improvements in treatment strategies are a continuous goal for treatment depression. Indeed, the overall number of remitters for medications is less

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		all tiers should be "insufficient" for both response rate and remission rate. The following 2010 publication reported the results of a multicenter clinical trial that utilized a sham rTMS treatment that was intended to produce the same sensations that the active rTMS treatment produced: George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, Anderson B, Nahas Z, Bulow P, Zarkowski P, Holtzheimer PE 3rd, Schwartz T, Sackeim HA, Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder. Arch Gen Psychiatry 2010; 67:507-516. The authors of the above publication concluded: "Although the treatment effect was statistically significant on a clinically meaningful variable (remission), the overall number of remitters and responders was less than one would like with a treatment that requires daily intervention for 3 weeks or more, even with a benign adverse effect profile".	than one would like but is not an argument not to treat with such an intervention.
Mark Demitrack, Neuronetics	Key Question 1	I have previously provided a dossier, acknowledged in the current draft report, that was submitted to Ms. Rose Campbell on 28 January 2009. I appreciate the care that was taken to include material from that dossier in the discussion and analyses included in the current draft version of the report. In addition to the material provided in my previous communication, there are now additional peer-reviewed scientific publications that will be of great interest to the authors and, which I believe, should be included in the final report in order to assure that the content of the report is as complete and accurate as possible at the time of its publication. Scientific work, specifically in the field of transcranial magnetic stimulation (TMS), is ongoing and the publications discussed below merit consideration by the authors in their deliberations.	We have created a new appendix to the report that comments on all studies mentioned here.
Mark Demitrack, Neuronetics	Key Question 1	In response to KQ1a, the authors should be aware that since the closure date of the literature review, an additional large, randomized, sham-controlled multi-site clinical trial has been completed and is now published in the peer-reviewed scientific literature (George, et al, 2010). Inclusion of this study will reinforce and strengthen the main conclusions of the authors' quantitative analysis regarding this Key Question. Therefore, it should be added to the report's analyses as it describes results from one of the largest TMS studies available and because it meets the AHRQ's criteria as a good quality, Tier 2 source study. This study is particularly important since it was an NIH-sponsored study, and was therefore conducted independent of industry support. In addition, this study incorporated several methodologic improvements on prior work, for example, the use of an active sham TMS control with rigorous attention to the integrity of study blinding. These investigators also focused on the primary	George, et al, 2010 – this studywas included during the update search phase post submission of the Peer Review Draft Demitrack and Thase, 2009 - this article was excluded due to the wrong publication type. The study pooled two studies for the analysis. The current review reviewed both studies pooled for analysis for inclusion in this report. One article, O'Reardon, 2007 } was included in our analysis. The second article, Avery, 2008 was excluded due to no comparison of interventions (all patients participating in the open-label study receive the same intervention).

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		efficacy endpoint of remission, measured using the 24 item Hamilton Depression Rating Scale (HAMD24), in order to clearly determine the clinical significance of the study outcome. Using the same device cleared for commercial use by the FDA and the same treatment parameters as reported in prior studies (Demitrack and Thase, 2009) these authors reported that there was a significant effect of active treatment on the proportion of remitters (15% active TMS vs 4% sham control group, P=0.015), representing a 4.2 times greater odds of reaching remission with active TMS compared to sham control. They concluded that *"...daily left prefrontal rTMS as monotherapy produced significant and clinically meaningful antidepressant therapeutic effects greater than sham..."* (George, et al, 2010). The authors should also consider that the inclusion of this study further underscores the point that there is now substantial evidence of the safety and efficacy of a specific, well-defined paradigm of TMS treatment for patients with treatment resistant depression, namely, high-frequency TMS delivered to the left dorsolateral prefrontal cortex of the brain. This specific TMS treatment paradigm is currently the only TMS paradigm that has assembled a sufficient body of evidence to result in clearance by the FDA for use in clinical practice.	Rumi et al 2005 - this study was not included in the current analysis due to inclusion of wrong population. The study makes no reference to the population as resistant or refractory, nor does it address prior treatment failure.	
Mark Demitrack, Neuronetics	Key Question 1	I believe that the Panel should also consider the report by Rumi and colleagues (2005) for inclusion as a good quality, Tier 3 source study in the analysis of KQ1b. As I was unable to review the Appendices of this draft report, I am not able to determine whether the Panel considered this study and determined that it was not eligible for inclusion. Inclusion of this study will reinforce and strengthen the main conclusions of the Panel's quantitative analysis regarding this Key Question. This study is a sham-controlled trial in 46 patients with major depression, randomized to receive either TMS or sham as an add-on treatment to amitriptyline pharmacotherapy. The TMS procedure involved 20 sessions administered as 5 pulses per second at 120% of motor threshold, for a total of 1250 pulses per treatment session. The primary hypothesis of this study was to determine whether TMS accelerates the onset of effect of amitriptyline therapy. As measured by the magnitude of reduction in the HAMD17 total score, patients randomized to the active TMS treatment arm demonstrated a statistically significantly superior benefit compared with sham beginning at week 1 and extending through the final observation at week 4.	Rumi et al 2005 study was not included in the current analysis due to inclusion of wrong population. The study makes no reference to the population as resistant or refractory, nor does it address prior treatment failure.	
Mark Demitrack, Neuronetics	Key Question 1	Within the context of answering KQ1b, the draft report reviews a substantial number of studies in order to arrive at best case estimates of "next step" pharmacotherapy outcomes in order to indirectly	Demitrack and Thase, 2009 This article was excluded due to the wrong publication type. The study pooled two studies for the analysis.	KQ1

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		compare next step pharmacotherapy with a non-pharmacological treatment for patients with TRD. On page 164, these data are summarized to indicate that estimates range from 16.8% to 25.3% for remission rates depending upon whether the "next step" pharmacotherapy option pursued is a switching, augmentation or maintenance strategy. The analysis notes that caution should be used in comparing these outcomes with non-pharmacologic outcomes. While I agree with the authors' cautious approach, I urge them to include a more substantive discussion of this comparative data for the interested reader, because of its instructive value. We believe this is appropriate in the case of TMS because of the enormity of the clinical trial data available to make this comparison. This data, which is obviously the substance of the answer to KQ 1a, involves estimates of response and remission outcomes from both randomized controlled trial data (Demitrack and Thase, 2009) and open-label clinical trial data (Avery, et al, 2008) that informs our understanding of the outcomes that can be expected with TMS. This methodologic strategy is also the subject of the report by Demitrack and Thase (2009). <u>References</u>: *Avery, DH, Isenberg, KE, Sampson, SM, et al. (2008) Transcranial magnetic stimulation (TMS) in the acute treatment of major depression: Clinical response in an open-label extension trial. J Clin Psychiatry, 69(3):441-451, 2008.* *Demitrack, MA, Thase, ME. (2009) Clinical Significance of Transcranial Magnetic Stimulation (TMS) in the Treatment of Pharmacoresistant Depression: A Review and Synthesis of Recent Data. Psychopharmacol Bulletin, 42(2):5-38.* *George MS, Lisanby SH, Avery D, et al. (2010) Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry 67(5):507-16.* *Rumi, DO, Gattaz, WF, Rigonatti, SP, et al. (2005) Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: A double-blind placebo-controlled study. Biol Psychiatry 57:162-166.*	The current review reviewed both studies pooled for analysis for inclusion in this report. One article, O'Reardon, 2007 was included in our analysis. The second article, Avery, 2008was excluded due to no comparison of interventions (all patients participating in the open-label study receive the same intervention).	

Mark Demitrack, Neuronetics	Key Question 2	I would like to thank the authors for including the data that was supplied in my original dossier in January, 2009 regarding the long term outcomes after acute response to TMS (Janicak, et al, citation #100, referenced in Table 45 in the draft report). I believe it would be important for the authors to update this reference with the now published final article of this work (Janicak, et al 2010), and to consider incorporating the additional information presented in this article in the discussion of KQ2. This complete publication expands the information contained in the initial citation, and includes additional information and analyses that are pertinent to the conclusions that can be drawn in response to KQ2. This study should be considered as a good quality, Tier 2 publication in the AHRQ report. Specifically, this more comprehensive report describes the clinical outcome during six months of follow up in a cohort of 99 patients who had benefited from acute treatment with to up to six weeks of TMS, and who then had successfully transitioned to maintenance antidepressant medication monotherapy during a 3 week transition. Long-term durability of effect was then examined over the subsequent six months. During this period of follow up, the chosen maintenance antidepressant medication protocol was structured by design and could not be switched or combined with other agents. However, TMS could be re-administered if patients met protocol-specified criteria for symptom re-emergence. Relapse was the primary outcome. In this analysis, 10 of 99 patients (10%; Kaplan-Meier survival estimate = 12.9%) met protocol-specified relapse criteria during the 6 months of follow-up. Thirty-eight (38.4%) met criteria for symptom worsening and 32/38 (84.2%) re-achieved symptomatic benefit with adjunctive TMS. The durability of effect reported following an acute response to TMS, including the relapse rates in longer term follow up compare favorably to a recent meta-analysis of 11 maintenance antidepressant treatment trials in unipolar depressed patients (Williams, et al, 2009). In that study, the authors reported a significant difference in relapse rates favoring active drug (i.e., 23%) versus placebo (i.e., 51%) over one year. The findings for TMS also compare favorably to reports with maintenance strategies after acute response to ECT. For example, Tew et al. (2007) reported on 73 unipolar depressed patients who achieved remission with acute ECT and were then randomized to maintenance treatment with nortriptyline monotherapy, nortriptyline plus lithium, or placebo for up to 6 months. The combination medication group experienced a 39% relapse rate	This reference was found to be eligible during the update search search phase after submission of the draft report for Peer Review., and the data has been updated from the recently published paper. Data from the older citation has been maintained in the evidence table since it describes a different subset of the population. The study is considered Tier 2, fair quality since the comparison is not randomized and conclusions are confounded by open label treatment with rTMS. Table 1 refers to the Kelner study which is ineligible for the review due to it not being a TRD population These data have been updated from the 2010 publication. Williams et al, (2009) this meta-analysis was not included in this review because it included populations that are not treatment-resistant. The authors clearly stated that three of the studies excluded treatment-resistant depression and seven studies had no criteria pertaining to TRD. Tew et al (2007) this study was excluded for wrong comparison. In this continuation study which would have been considered for key question 2, the study only compares pharmacotherapy to treatment as usual which is not a comparison of interest for this key question. Sackeim (2001) --This study was not included for Key Question 1b (pharmaceutical analysis) because the population did not meet the criteria of 2 or more treatment failures. Key Question 1b required included populations to have 2 or more treatment failures.

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		versus 60% for those on nortriptyline only and 84% on placebo. These results were virtually identical to an earlier report by Sackeim and colleagues (2001) in a group of 83 unipolar depressed patients followed for up to 24 weeks after achieving remission to an acute course of ECT. Finally, the Consortium for Research in Electroconvulsive Therapy (CORE) reported the relapse rates over 6 months in 201 acute ECT responsive, unipolar depressed patients maintained on either continuation ECT (i.e., 37.1%) or continuation (i.e., lithium plus nortriptyline) (i.e., 31.6%) (see Table 1 below). References: *Janicak, PG, Nahas, Z, Lisanby, SH, et al. (2010) Long-Term Durability of Acute Response to Transcranial Magnetic Stimulation (TMS) in the Treatment of Pharmacoresistant Major Depression. Brain Stimulation, 3:187-199.* *Kellner, CH, Knapp, RG, Petrides, G, et al. Continuation Electroconvulsive Therapy vs Pharmacotherapy for Relapse Prevention in Major Depression: A Multisite Study From the Consortium for Research in Electroconvulsive Therapy (CORE). Arch Gen Psychiatry 2006, 63:1337-1344*	Janicak, (2010) Included during the update search phase post submission of the Peer Review Draft; it is rated as a fair quality study Kellner, 2006 - This study was excluded for not meeting criteria for a treatment resistant population. The article states that only 42.7 percent of a portion of the population rated (using the ATHF) as having had at least one adequate failure. This indicates that 57.3 percent of this population did not have at least one treatment failure. The entire population, therefore, cannot be considered treatment-resistant by this review's definition.
Mark George	Key Question 2	With respect to long-term durability of VNS, or TMS, the report does cite the longest VNS study to date, with a comparator group of TRD patients getting medication changes. 2 This study is cited, but only for side effect data and the important information concerning one-year clinical outcomes of VNS compared to changing medications is not cited or analyzed or listed in the tables. This study suggests that VNS has a slow onset of response, but that responses are durable, and that the clinical effects are better than medication changes in patients with TRD.	George 2005; Excluded from KQ2 for wrong study design (observational study). The protocol for this review states that only randomized controlled trials and meta-analyses are eligible study designs for this key question.
NIMH	Key Question 2	The review notes that little evidence is available regarding the comparative efficacy of nonpharmacologic interventions in maintenance of remission or relapse prevention. For this section, it would be helpful to mention the NIMH-supported study on comparison of maintenance ECT versus pharmacotherapy as continuation treatments following the successful induction of remission with an acute course of ECT. Both interventions proved equally effective in relapse prevention. ***Reference:*** Kellner CH, Knapp RG, Petrides G, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: A multisite study from the Consortium for	Kellner (2006) was excluded for not meeting criteria for a treatment resistant population. The article states that only 42.7 percent of a portion of the population rated (using the ATHF) as having had at least one adequate failure. This indicates that 57.3 percent of this population did not have at least one treatment failure. The entire population, therefore, cannot be considered treatment-resistant by this review's definition.

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		Research in Electroconvulsive Therapy (CORE). *Arch Gen Psychiatry* 2006; 63:1337–1344.	
NIMH	Key Question 2	The review notes that the issue of duration of treatment effect is little documented in nonpharmacologic treatments of depression. In this area of research, an important NIMH-supported contribution is the work of Sackeim and colleagues who reported that combined nortriptyline plus lithium was superior to nortriptyline alone in preventing relapse during a 6-month follow-up after a successful acute course of ECT. A striking study finding was that the placebo-control group experienced a relapse rate greater than 80% during follow-up. These results established the necessity of active continuation treatment. ***Reference:*** Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: A randomized controlled trial. *JAMA* 2001; 285:1299-1307.	Sackeim (2001)This study was not included for Key Question 1b (pharmaceutical analysis) because the population did not meet the criteria of 2 or more treatment failures. Key Question 1b required included populations to have 2 or more treatment failures.
NIMH		Another recent paper worth citing is the continuation phase of the large industry-sponsored rTMS trial that is referenced in the review regarding short-term findings. Earlier this year, Janicak and colleagues published the results of a 6-month naturalistic follow-up of this cohort, successfully using re-institution of rTMS as an "intermittent rescue strategy" to preclude impending relapse in some patients. ***Reference:*** Janicak PG, Nahas Z, Lisanby SH, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: Assessment of relapse during a 6-month, multisite, open-label study. *Brain Stimulation* 2010; 3:187-199.	Janicak (2010) – We agree and the study was included during the update search phase post submission of the Peer Review Draft
Mark Demitrack, Neuronetics	Key Question 3	I appreciate the authors' comments that there is limited information in the published scientific literature to address this question. Though I have no additional information to add from our existing studies, I would like to reiterate the points I made in the dossier submitted to the Panel in January, 2009: *"In our clinical development program, we have reported clinical outcomes for specific symptom subtypes represented by standard factor scores measured on the Hamilton Depression Rating Scale. Efficacy of the NeuroStar TMS system on patient outcomes across these specific symptom subtypes represented on the HAMD Factor Scores was reported in the outcomes for Study 101 contained in the O'Reardon, et al (2007) publication. These data demonstrated statistically significant benefit*	O'Reardon (2007) - The data that is reported in the study did not allow us to specifically identify the subgroup with the anxiety symptom cluster.

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		in favor of the active TMS treatment group compared to the sham TMS treatment group at both the week 4 and week 6 outcome time points on the Factor Scores for Core Depression Symptoms, the Maier and Gibbons Depression Factor Scores, the Anxiety/Somatization Factor Score, and the Psychomotor Retardation Factor Score. There was no difference on the Sleep Factor Score, indicating that TMS does not exert a soporific effect during acute treatment." Reference: *O'Reardon, JP, Solvason, HB, Janicak, PG, et al. (2007) Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multi-Site Randomized Controlled Trial. Biol Psychiatry, 62:1208-1216.*	
Mark Demitrack, Neuronetics	Key Question 4a	In answer to KQ4a, I would like to draw the authors' attention to additional data that has been reported since the closure of the data review. Specifically, we have now reported the cognitive function outcomes of a large cohort of patients treated with the clinically established TMS protocol of high frequency, left prefrontal cortex stimulation (Demitrack, et al, 2009). In this study, cognitive function was examined in a multisite, randomized controlled trial of TMS in patients with pharmacoresistant MDD (O'Reardon, 2007) (N=155 active TMS, N=146 sham TMS). Specific measures of global cognition (Mini Mental Status Examination, MMSE), short-term (Buschke Selective Reminding Test, BSRT) and long-term (Autobiographical Memory Interview-Short Form, AMI-SF) memory were obtained prior to first treatment, and at 4 and 6 weeks during an acute treatment course of daily, left prefrontal TMS. There was no deterioration of cognitive function within or between treatment groups on any measure of cognition during acute treatment. Additionally, each treatment group was stratified by clinical outcome (HAMD24 responder) at the end of 6 weeks. Within the TMS group only, there was a statistically significant improvement on the BSRT in the TMS responders compared to TMS non-responders for both short-term recall (P = 0.0116 at 4 weeks; P = 0.0038 at 6 weeks) and delayed recall (P = 0.0463 at 4 weeks; P = 0.0012 at 6 weeks). This improvement in cognitive function was not seen in sham treated patients (P = NS at both 4 and 6 weeks). These results further strengthen the conclusions within the AHRQ draft report and are consistent with the view that clinical recovery with active TMS is associated with an improvement in short-term verbal	Demitrack (2009) - This article was excluded due to the wrong publication type. The study pooled two studies for the analysis. The current review reviewed both studies pooled for analysis for inclusion in this report. One article, O'Reardon, 2007{O'Reardon, 2007 #79} was included in our analysis. The second article, Avery, 2008{Avery, 2008 #42} was excluded due to no comparison of interventions (see number 2 above).

		memory that cannot be fully accounted for by improvement in mood. These findings are based on a good quality, Tier 2 study and should be considered for inclusion in the final report for KQ4a.	
Mark Demitrack, Neuronetics	Key Question 4	While I recognize that there is a paucity of information from randomized, sham-controlled trials in the recent literature regarding the specific adverse event profile of ECT, I believe that the representation of the potential cognitive consequences of ECT could be further informed by considering several additional recent sources of data. In so doing, I believe the AHRQ report would be strengthened and provide the reader a more comprehensive and clinically meaningful, albeit indirect, ability to compare and contrast the potential cognitive consequences of ECT in comparison to other non-pharmacologic treatments such as TMS. While some of these studies may not meet the stringent study selection criteria, I believe the clinical importance and authoritative character of these references merits inclusion in authors' discussion, and indeed their absence is conspicuous, and potentially leads the reader to minimize the devastating cognitive consequences of ECT as a non-pharmacologic option. For example, I believe it would be appropriate to reference for the reader such sources as the authoritative Task Force report from the American Psychiatric Association (2001). Also, reference to the substantial, contemporary body of work from the investigative group at Columbia University should somehow be incorporated into the Panel's discussion. As an example, the study by Sackeim and colleagues (2007) is one of the largest and only studies to address the question of persistent and long-term cognitive sequelae from ECT. Other important relevant references from the Columbia group are listed below (Lisanby, et al, 2000; Sackeim, et al, 2000).	American Psychiatric Association (2001) This reference is a set of guidelines. Guidelines do not fit the inclusion criteria for appropriate publication types. The guidelines were not included in the analysis of this review. Lisanby (2000) This study was excluded from the analysis. The study performs its analysis on right unilateral compared to bilateral electrode placement for electroconvulsive therapy. It also compares low versus high electrical dosage. Neither of these comparisons are comparisons of interest for this review. Sackeim (2007) This study was not included in the current analysis because the analysis does not include a comparison. The study compares baseline and post-treatment outcomes after electroconvulsive therapy. Sackeim (2000) This study was not included in the current analysis because the analysis does not include a comparison of interest. The study compares right unilateral ECT at three different thresholds to bilateral ECT at one threshold. There is no other intervention comparison.
Mark Demitrack, Neuronetics	Key Question 4a	In response to KQ4a, I believe there may be studies that the authors have overlooked that would be relevant to include in their analysis and discussion of the potential cognitive consequences of TMS. Without the ability to view the Appendices to the report, it is not clear to me whether these studies were considered and did not meet the AHRQ standard for inclusion. Nevertheless, I provide information on these references for the Panel's consideration. These studies include the prospective cohort report by Martis and colleagues (2003), and the randomized controlled trial by Hausmann and colleagues (2004). Both of these studies serve to strengthen the overall conclusions of the Panel that TMS should be considered	Martis (2003) -This article was excluded from this review due to no comparison. This article, although part of a larger randomized controlled trial, only reports on those persons receiving rTMS. The study does not report on any comparison intervention. Hausmann (2004) This study was excluded from analysis as it is not apparent that the population is treatment resistant. The article does not refer to the population as resistant or refractory, nor does it discuss prior

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		either cognitively neutral or beneficial with regard to specific measured domains of cognitive function.	treatment failures of the included population
Mark Demitrack, Neuronetics	Key Question 4b	In response to KQ4b, I believe there are relevant studies that have been overlooked. Specifically, the reported adverse event experience with TMS is now very well established in the two large, randomized, sham-controlled clinical trials that have been completed with the most commonly used TMS treatment protocols (O'Reardon, et al, 2007; Janicak, et al, 2008; George, et al, 2010). In fact, the Janicak, et al (2007) report is the most authoritative, complete, peer-reviewed summary of the adverse event experience from the O'Reardon, et al clinical study, and in addition includes the adverse event experience observed during the 6 month long-term follow-up phase of that study. None of this information is included the answer to KQ4b. These studies would most appropriately be considered as good quality, Tier 2 studies and therefore should be analyzed as part of the information included in Table 64, page 126. The strength of the evidence derived from these two studies should be recognized as particularly informative to KQ4b in part because they are among the few studies that incorporated standardized methods of adverse event data collection and terminology coding using contemporary accepted standards of adverse event reporting, i.e., the MedDRA Coding Thesaurus. In fact, inclusion of this data would dominate the sample database upon which to draw definitive conclusions about the safety of TMS. It is also important to note that these data render irrelevant the suggestion that TMS may be associated with the development of difficulty starting urination. This adverse event has only been reported in one study, namely, the small study by Berman, et al (2000). I would like to point out that even in that report the authors noted that this event was shown to be statistically insignificant when analyses were corrected for multiple comparisons. This event was not present as a device-related adverse event in either of the large, multisite randomized controlled trials, nor is there any physiologically plausible reason to expect that such an event would occur with TMS treatment. I believe that consideration of this information should lead the authors to consider revising its conclusions in specific areas of the report, such as in Table 97, page 160-1, where the statement is made that the strength of evidence is low to allow conclusions to be drawn regarding the type and severity of adverse events observed in TMS	George, et al, (2010) was included during the update search phase post submission of the Peer Review Draft Janicak et al 2008 This article is included in the present analysis Janicak et al (2007) This article is included in the present analysis. O'Reardon (2007) This study is included in the current analysis. It is not included for Key Question 3 (symptom subtypes). Symptom subtypes represented by standard factor scores measured Berman, (2000) This study in included in the present analysis

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		vs sham clinical trials. In my view, the aggregate evidence on this point is now large and very reproducible across studies. References: *American Psychiatric Association Task Force Report on Electroconvulsive Therapy (second edition) Weiner, RD, Coffey, CE, Fochtmann, LJ, et al (eds), (2001)* *Demitrack, MA, Loo, C, Maixner, DF, et al. Transcranial Magnetic Stimulation (TMS) in the Treatment of Pharmacoresistant Major Depression: Examination of Cognitive Function During Acute Treatment. Presented at the Society for Biological Psychiatry Annual Meeting, Vancouver B.C., May, 2009 and at the New Research Sessions of the American Psychiatric Association Annual Meeting, San Francisco, California, May, 2009.* *Hausmann, A, Pascual-Leone, A, Kemmler, G, et al. (2004) No deterioration of cognitive performance in an aggressive unilateral and bilateral antidepressant rTMS add-on trial. J Clin Psychiatry 65(6):772-782.* *Janicak, PG, O'Reardon, JP, Sampson, SM, et al. (2008) Transcranial magnetic stimulation (TMS) in the treatment of major depression: A comprehensive summary of safety experience from acute and extended exposure and during reintroduction treatment. J Clin Psychiatry, 69(2):222-232.* *Lisanby, SH, Maddox, JH, Prudic, J, et al. (2000) The effects of electroconvulsive therapy in memory of autobiographical and public events. Arch Gen Psychiatry 57:581-590.* *Martis, B, Alam, D, Dowd, SM, et al. (2003) Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. Clin Neurophysiol 114:1125-1132.* *O'Reardon, JP, Solvason, HB, Janicak, PG, et al. (2007) Efficacy and Safety of Transcranial Magnetic Stimulation in the Acute Treatment of Major Depression: A Multi-Site Randomized Controlled Trial. Biol Psychiatry, 62:1208-1216.* *Sackeim, HA, Prudic, J, Devanand, DP, et al. (2000) A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. Arch Gen*	

		Psychiatry 57:425-434. *Sackeim, HA, Prudic, J, Fuller, R, et al. (2007) The cognitive effects of electroconvulsive therapy in community settings. Neuropsychopharm 32:244-254.*	
Mark George	Key Question 4	The report does not cite the most recent worldwide safety and side effect study of TMS. 3 The note about TMS causing urinary hesitancy is not found in any other studies and was not found in the large industry TMS trial or the OPT-TMS trial. (I have never encountered this side effect in any TMS study or patient in my 17 years of research with the technology.) Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2009	Rossi (2009) This study was not included in the current analysis because it does not represent a publication type of interest. The reference is cited within the text of the current review.
Mark Demitrack, Neuronetics	Key Question 5	I appreciate the authors' comments that there is limited information in the published scientific literature to address this question. Though I have no additional information to add from our existing studies, I would like to reiterate the points I made in the dossier submitted to the Panel in January, 2009: *"We have performed a detailed analysis for predictors of clinical outcome to the NeuroStar TMS system. This analysis is reported in Lisanby, et al (2009). Results of that work show that the sole pre-treatment patient clinical characteristic that serves as a statistically significantly predictor of efficacy outcome in the randomized controlled trial, Study 101, was the prior level of antidepressant treatment resistance in the current illness episode, as defined by the ATHF. Specifically, those patients who failed to receive satisfactory clinical benefit, in current illness episode, from* ***one ATHF-verified antidepressant treatment exposure****, showed a superior clinical outcome compared to those patients with greater levels of treatment resistance. At this time, the small size of the study sample and resulting limitations of statistical power in the more severe grades of treatment resistance precludes a definitive conclusion regarding clinical benefit in patients who have failed to achieve satisfactory clinical benefit from more than one ATHF-verified treatment exposure in their current illness episode.* *No other benefits or treatment harms were evident in other clinically*	Lisanby et al (2009) This study was excluded for wrong outcome. The study attempts to determine predictors of outcomes which is not an outcome of interest for this review

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		notable subpopulations. We specifically examined and found no evidence of differences in outcome based age, and gender. Specific evidence of benefit or harm in medically comorbid subpopulations was not examined in detail as this was not a focus of the present studies. Nevertheless, it is worth pointing out that because of its non-invasive and anatomically localized nature, TMS is devoid of systemic adverse events, and therefore lacks the toxicities of more complex antidepressant pharmacotherapies or the surgical risks associated with other more invasive device-based treatment modalities. Therefore, TMS may have certain unique clinical advantages in high-medical risk populations." References: *Lisanby, SH, Husain, MM, Rosenquist, PB, et al. (2009) 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. Neuropsychopharm, 34:522-534*	
Mark Demitrack, Neuronetics	Key Question 6	In the original Key Question text, the question also appeared to incorporate an analysis of potential health economic differences across various non-pharmacologic treatments. It is not clear to me why this aspect of the answer to KQ6 has been removed, as I believe there is useful and interesting data in the peer-reviewed scientific literature on this point. In my original dossier, we noted this by including an in press reference (Simpson, et al, 2009), which the Panel has cited in their discussion of TMS on page 23 of the current draft report. I believe the answer to this question would be strengthened by again including information on comparative health economics of non-pharmacologic treatments, since the peer-reviewed published literature has continued to grow on this topic, the majority of which would be considered good quality, Tier 1 and 2 reports from the AHRQ perspective. In fact, there are several important sources of peer-reviewed scientific literature that have addressed this question. For instance, Kozel and co-workers (2004) performed an analysis of the cost-effectiveness of TMS compared with ECT in patients with severe depression who failed to benefit from prior pharmacotherapy. Their analysis provided support for an economic benefit, concluding that TMS alone offers a considerable advantage over ECT alone in these patients. They also found that TMS followed by ECT for patients who did not adequately respond to acute TMS also had an	Simpson (2009) This study was not included in the current analysis for reporting outcomes that were not of interest for the current review. The study performs cost-effective analyses. Please note the study is cited in the text of the review. Fava (2006) This study was included in the Key Question 1b analysis (pharmaceutical interventions). Because it is comparing to pharmaceutical interventions it was only eligible to be included in Key Question 1. While we appreciate that cost effectiveness is an important outcome, it is not one of the outcomes relevant to these particular key questions.

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		economic benefit, showing an increase in quality adjusted life years (QALYs) compared with the use of ECT alone. This result is due to a proportion of patients benefiting from TMS as an alternative treatment option with reduced morbidity and hence increases in QALYs, who otherwise would have only had the option of receiving ECT, whose QALY outcomes in this analysis are negatively influenced by the morbidity of the procedure itself. In the report by Kozel and colleagues (2004), sensitivity analyses of the model studied indicated that the outcomes were robust across a broad range of parameters. This included variations in the assumed clinical benefits of TMS, and over a substantial range of estimates of the assumed reimbursed cost of TMS treatment. In a recent independent report, Nelson and colleagues (2009) systematically reviewed all MEDLINE-cited cost utility analyses published in English between 2002 and 2007, with the intent of identifying cost-and quality-decreasing medical innovations that would offer favorable, "decrementally" cost-effective tradeoffs. They defined a decrementally cost effective innovation as one that saves money, but may be less effective, compared with the alternative option studied. Of 2,128 cost-effectiveness ratios from 887 publications, TMS as an alternative to ECT was one of only nine such decrementally cost-effective medical innovations, with an estimated savings of $US 11,672 associated with a clinically negligible QALY loss estimated at 0.0212. In clinical terms, this outcome acknowledges that available data supports the view that while TMS generally is reported as a somewhat less effective treatment than ECT for non-psychotic pharmacoresistant major depression, it is procedurally less cumbersome and costly to implement. As I have stated in my dossier submitted in January, 2009, using an updated evidence base for TMS, Simpson and colleagues (2009) examined the cost-efficacy of TMS compared with complex pharmacotherapy using a decision analysis model. This approach considered the cost outcomes from an acute treatment course of either intervention (TMS or complex pharmacotherapy) and the subsequent costs of a full year of treatment follow-up in the analysis. This report then compared the cost-effectiveness of TMS as observed in the recently published results of the clinical registration studies that led to FDA clearance in the US (Demitrack and Thase, 2009; O'Reardon, 2007) to data from the STAR*D Study Levels 2 and 3 outcomes as a best estimate of the costs and outcomes of pharmacotherapy as usual (Fava, 2006; Nierenberg, 2006; Rush,	

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		2006; Trivedi, 2006). The analysis showed that TMS, at an assumed reimbursed cost of $US 300 per treatment session, resulted in a net cost savings of $US 1,123 per QALY gained when compared to standard of care pharmacotherapy. The savings increased further when the estimated costs of productivity gains were included in the model, resulting in a net savings of $US 7,621. Based in part on this information, I would like to request that the authors consider re-instating a general discussion of the topic of health economic consequences of non-pharmacologic treatments in the final report in the answer to KQ6. *Demitrack, MA, Thase, ME. (2009) Clinical Significance of Transcranial Magnetic Stimulation (TMS) in the Treatment of Pharmacoresistant Depression: A Review and Synthesis of Recent Data. Psychopharmacol Bulletin, 42(2):5-38.* *Fava, M, Rush, AJ, Wisniewski, et al. (2006) A Comparison of Mirtazapine and Nortriptyline Following Two Consecutive Failed Medication Treatments for Depressed Outpatients : A STAR*D Report. Am J Psychiatry. 163:1161-1172.* *Kozel, FA, George, MS, Simpson, KN. (2004) Decision Analysis of the Cost-Effectiveness of Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy for Treatment of Nonpsychotic Severe Depression. CNS Spectrums 9(6):476-482.* *Nelson, AL, Cohen, JT, Greenberg, D, Kent, DM. (2009) Much Cheaper, Almost as Good: Decrementally Cost-Effective Medical Innovation. Ann Int Medicine 151:662-667.* *Nierenberg, AA, Fava, M, Trivedi, MH, et al. (2006) A Comparison of Lithium and T3 Augmentation Following Two Failed Medication Treatments for Depression: A STAR*D Report. Am J Psychiatry. 163:1519-1530.* *Rush, AJ, Trivedi, MH, Wisniewski, SR, et al. (2006) Bupropion-SR, Sertraline, or Venlafaxine-XR after Failure of SSRIs for Depression. N Eng J Med, 354(12):1231-1242.* *Simpson, KN, Welch, MJ, Kozel, FA, et al. (2009) Cost-Effectiveness of Transcranial Magnetic Stimulation in the Treatment of Major Depression: A Health Economic Analysis. Adv Ther 26(3):346-368.*	

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		Trivedi, MH, Fava, M, Wisniewski, SR, et al. (2006) Medication Augmentation after the Failure of SSRIs for Depression. N Eng J Med, 354(12):1243-1252.	
Peer Reviewer #1	Discussion	The major findings about the overall evidence for efficacy of each intervention and the limited high quality data available to compare those interventions are clearly stated. Limitations of the studies as well as the review are clearly stated. The discussion does not omit any important literature to the best of my knowledge. The future research section clearly calls for the types of research that should be done in the future to inform clinicians.	Thank you.
Peer Reviewer #2	Discussion	The broad messages that future investigators should choose a standard definition of TRD and engage in better reporting of numbers of treatment failures could be heard clearly.	Thank you.
Peer Reviewer #2	Discussion	The future research section is very informative. It was easy to follow the logic of why the recommendations are important.	Thank you.
Peer Reviewer #3	Discussion	The implications are clear and on target. The future research section provides clear direction for what needs to be done.	Thank you.
Peer Reviewer #4	Discussion	In the summary table (included in the executive summary and discussion sections) it could be informative to describe sample sizes or give some other indicator of precision. This would be especially useful for interpreting findings of no difference (either treatment A is not superior to sham/placebo OR treatment A does not differ significantly from treatment B). This information is provided in the main report, but some (if only brief) indicator of precision would be useful in the executive summary.	We agree, and we have added a sample size column to these summary tables.
Peer Reviewer #5	Discussion/ Conclusion	I think overall, with the exception of the aforementioned, the authors do a nice job of describing the major implications of the evidence and the limitations of the literature thus far. Their call for action, such as more uniformity in diagnosis and in therapeutic protocols, is well thought out and will help the field progress by laying the groundwork for future research endeavors.	Thank you.
Peer Reviewer #5	Discussion/ Conclusion	It was not clear to me why the authors did not say more about interpersonal therapy. They mention it along with CBT as an evidence-based therapy for depression but then never describe it in further discussion. It's possible that the authors could not find the use of IPT in TRD but it would be good to state that.	We agree that interpersonal therapy (IPT) is an important clinical consideration, but we found no IPT trials that met our inclusion criteria. We have added in the Discussion section that we identified no eligible IPT studies in TRD.

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Peer Reviewer #6	Discussion/ Conclusion	Page 24 in the right column "In post-stroke depression, rTMS groups had significantly better depressive severity than sham groups" This is confusing--did they have more depression or less or more reduction.	This has been corrected to indicate a greater decrease in depressive severity.
Peer Reviewer #6	Discussion/ Conclusion	Page 183 "Follow-up periods were generally short than desirable" should be "shorter"	Correction made.
Peer Reviewer #7	Discussion/ Conclusion	The implications of the major findings are clearly stated. The limitations of the review/studies are described adequately. In the discussion, did the investigators did not omit any important literature.	Thank you.
Peer Reviewer #7	Discussion/ Conclusion	The future research section is clear and easily describes new research directions.	Thank you.
Peer Reviewer #9	Discussion	The call to arms for further research is clear and compelling, although as stated above, RCTs of sufficient size will be difficult to fund and execute.	We agree that funding for many forms of research remains challenging.
Peer Reviewer #9	Discussion	The basic findings- that there is really not enough high quality evidence to support any one of the treatments over any others has important implications for clinicians. Given the difference in costs of some of these treatments I would like to have seen more guidance for the clinician and patient, taking these considerations in mind. Perhaps this review could add a brief chapter for clinicians, including an admonishment about making sure two adequately dosed trials of antidepressants have been completed.	We agree that this kind of review is important. The Eisenberg Center will be creating this product.
Peer Reviewer #11	Discussion	I'm still not clear on the major take home point. The conclusion that "Comparative clinical research on nonpharmacologic interventions in a TRD population is early in its infancy" is misleading since it ignores the studies comparing the efficacy of different forms of ECT in this population. I don't think this will usefully guide clinical practice, since the reader may come away from this thinking there are no proven treatments for TRD, when in fact there is - namely ECT.	The purpose of this Comparative Effectiveness Review is to compare different non-pharmacologic treatments, not to compare different forms of ECT. The latter, while important, is out of the scope of this CER. We believe that the review fairly reflects the current state of evidence regarding ECT in the TRD population. The limited data we found regarding ECT in TRD populations was consistent with findings in a 2003 systematic evidence review in the Lancet (Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. The UK ECT Review Group Lancet 2003; 361: 799–808). The efficacy of ECT in depression is not in

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			question, but the clinical trial evidence specifically for TRD is limited.
Mark Demitrack, Neuronetics	Discussion	Page 169: The reference is made that if TMS is not demonstrating efficacy at two weeks of treatment, then consideration should be given to switching treatments. This statement should either be revised to be consistent with current minimum duration of treatment as articulated in FDA-cleared product labeling (i.e., 4 weeks), or deleted.	We have removed the reference here to rTMS.
Mark Demitrack, Neuronetics	Discussion	Page 171: I would take issue with the statement that the clinically recommended TMS protocol is still "in the process of being developed". In fact, the vast majority of the studies, and the current FDA-cleared treatment protocol is well-validated and established, namely the use of high-frequency, left prefrontal cortex administration of TMS with a specific TMS stimulation parameter set. Nevertheless, it is true that TMS, like every other known antidepressant treatment both pharmaceutical and non-pharmaceutical, does not work in all cases, and therefore clinical research is constantly exploring additional strategies that may enhance the likely benefit from any treatment.	We have modified this statement to note that standardization had been difficult while the protocol wqs being developed, but that now standardized protocols should be followed.
Peer Reviewer #4	Conclusion	The conclusion sections (of both the executive summary and the main document) might distinguish between absolute effectiveness (For which interventions do we have adequate evidence for effectiveness compared to a no-treatment, placebo or sham treatment?) and comparative effectiveness (For which comparisons of alternative "active" treatments do we have adequate evidence?).	We appreciate the suggestion. We agree that this is an important distinction. We currently make this distinction in our stratification into "Direct Evidence" (analogous to "comparative effectiveness") and Indirect Evidence (analogous to "absolute effectiveness"). In the interests of clarify and to avoid introducing new potentially confusing terms, we will leave as is.
Peer Reviewer #1	General	This comprehensive report covers the extant but limited literature on non-pharmacologic interventions for treatment resistant depression. As stated by the authors, the lack of a sufficient database that compares the interventions prevents any clinical meaningful conclusions that could guide clinicians. Yet, at the same time, the overview can be quite useful to the target audience, which is explicitly defined. The key questions are appropriate and explicitly stated.	Thank you.
Peer Reviewer #2	General	The report is highly clinical relevant. Whether clinicians will be able to extract information that will influence their practices at this time is not immediately apparent. The likelihood that clinicians and others will easily extract useful data is probably not increased by having essentially 6 "populations" (MDD alone /some portion BD x three levels of treatment resistance)	We agree that the degree of stratification makes the take away points more confusing, and we have now limited the Strength of Evidence assessment to Tier 1 studies in the Results, and have limited our summary of findings in the Discussion and Executive Summary sections to TRD studies (Tier 1).

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			Also, the Eisenberg Center will help produce a summary of more direct use to clinicians and other decision makers.
Peer Reviewer #3	General	This is a well done, well-constructed review of a rather limited literature. The authors do a good job of covering the relatively small number of studies that have been done and comment appropriately on the marginal quality of those trials and what should be done to improve the informativeness of the literature.	Thank you.
Peer Reviewer #4	General	Questions are clearly stated, and they seem (at least to me) the right questions.	Thank you.
Peer Reviewer #5	General	The report is meaningful. It clearly defines the target population of treatment-resistant depression and discusses the heterogeneity involved in this diagnosis. It appears to help set a standard to be used going forward--failure to respond to two or more antidepressants. This is a major public health problem that the report helps to focus attention on.	Thank you.
Peer Reviewer #6	General	Please revise my information: Medical Director of Center for Integrative Medicine, University of Pittsburgh Medical Center Department of Psychiatry, University of Pittsburgh Medical Center, Pennsylvania Should be Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA	Correction made.
Peer Reviewer #7	General	The report is clinically meaningful and the target population and audience explicitly defined.	Thank you.
Peer Reviewer #7	General	The key questions are appropriate and explicitly stated.	Thank you.
Peer Reviewer #8	General	What I have to contribute comes from a view of the document as methodologically rich but conceptually poor in ways that I think need some attention.	Peer reviewer # 8 had many observations related to the complexity of treatment resistant depression and offers a number of important insights. We agree that TRD is conceptually complex. However, the definition of TRD was limited by how it has been operationally defined in the available research data base. While clarifying the most accurate definition of TRD is greatly important, this aim is outside the scope of the current CER.

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			In response to this and other comments, however, we have further clarified the complexity of TRD in the Introduction and Discussion
Peer Reviewer #8	General	It is increasingly clear that the problem of treatment resistance is one that cuts across disorders. As we develop evidence-based treatments, we learn not only of the efficacy of evidence-based treatments, but also of their severe limitations, and that substantial numbers of patients across a range of disorders fail to benefit from our best treatments. Our diagnostic manual and our field's approach to the study and use of treatment interventions tend to assume patients have one disorder at a time, but this assumption may not be true, especially among those who fail treatment. Although there is no doubt that single disorder treatment resistance exists, it is not clear that approaching the problem of treatment resistance this way offers the best grasp of the scope of the problem—particularly as evidence of the role of other issues in treatment resistance emerge, such as comorbidity or early trauma, loss, deprivation or neglect. Let me make my overall point by quoting from a book I am editing entitled *Treatment Resistance and Patient Authority: The Austen Riggs Reader*, to be published by W. W. Norton in spring 2011. Chapter 1, by J. Christopher Fowler, Eric M. Plakun and Edward R Shapiro, takes a broad view of the scope of the problem of treatment resistance and, among other things, notes the following:	See above.
Peer Reviewer #8	General	Elsewhere in the chapter [if you wanted a copy of the entire chapter I could arrange it] we comment on studies you appear not to have reviewed that raise other important questions. For example Leichsenring and Rabung [JAMA, 2008] performed a meta-analysis of 23 studies involving over a thousand patients with complex comorbid disorders who had failed to benefit from previous treatment. Many of these patients would qualify as having treatment resistant depression. On average, they responded better to long-term dynamic therapy than to other interventions [the average patient receiving long-term dynamic therapy was better off than 96% of patients receiving other treatments]. Although this study would not meet Tier 1 standards, a reasonable clinician or researcher would nevertheless want to know about it and want to pursue further study of this treatment intervention. I suspect you are familiar with the challenge of funding psychodynamic therapy research in this country	See above. Note that the JAMA study cited here does not include a TRD population and would not be eligible for our CER. We will identify this article in the appendix.
Peer Reviewer #8	General	Nemeroff [et al., PNAS, 2003—and Michael Thase was a co-author] studied a large cohort of chronically depressed patients who had failed multiple treatments. In this sample, patients with histories of	We will identify this article in the appendix. This article does not meet the definition of TRD (number of prior treatments not

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		early adverse events responded better to the form of CBT tested than to any drug intervention. The authors raise the question of whether psychotherapy is an essential ingredient in the treatment of depressed patients like these who have histories of early trauma, abuse, neglect, loss or deprivation.	described and not a part of eligibility criteria for study).
Peer Reviewer #8	General	The information provided here would not likely lead to new conclusions for the document under review, but might well lead to a significant broadening of the scope of questions raised for further study. Additional questions that might be included in the document include the following: ▪ Given evidence that multiple factors beyond meeting the criteria for depression may be associated with treatment resistance, should any definition of TRD include severity, chronicity, comorbidity and psychosocial dimensions of the degree of impairment?	We appreciate the reviewer's suggestion, but we are not able to expand the scope of the key questions. We have further emphasized the complexity of TRD in the Limitations to the Evidence Base and in Future Research Needs.
Peer Reviewer #8	General	The information provided here would not likely lead to new conclusions for the document under review, but might well lead to a significant broadening of the scope of questions raised for further study. Additional questions that might be included in the document include the following: ▪ Should we work toward a definition of treatment resistance that cuts across disorders?	See above.
Peer Reviewer #8	General	The information provided here would not likely lead to new conclusions for the document under review, but might well lead to a significant broadening of the scope of questions raised for further study. Additional questions that might be included in the document include the following: ▪ Should the document more clearly call for research into the phenomenology of treatment resistance as a function of comorbidity?	See above.
Peer Reviewer #8	General	The information provided here would not likely lead to new conclusions for the document under review, but might well lead to a significant broadening of the scope of questions raised for further study. Additional questions that might be included in the document include the following: ▪ Should the document note the evidence suggesting psychodynamic therapy may be particularly useful for complex comorbid patients and call for research into this challenging group of patients.	See above.
Peer Reviewer #9	General	I find this review to be extremely helpful for the research community as a call to arms for further research to better inform practice. The questions are appropriate and well-defined. However, because of the current paucity of studies in this area, there is very little information in	Thank you.

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		the review to help clinicians- in collaboration with patients- make decisions about options for care in "true" TRD.	
Peer Reviewer #11	General	The review appears to ignore the wealth of evidence about the efficacy of ECT in TRD. For example, the tables in the overview focus only on ECT vs meds or ECT vs rTMS. However, there are actually ECT vs sham trials, and trials that contrast ECT with an active control (low dose right unilateral ECT can be considered a control condition because of the low efficacy see with this modality in comparison with high dose right unilateral and bilateral ECT). This is a serious limitation of this work since it ignores the wealth of data on the efficacy of ECT, and collapses across all modalities of ECT which obscures the clinical reality that the efficacy and safety of ECT is highly dosage dependent. The conclusion that there is no convincing evidence for differential cognitive effects of ECT vs TMS also flies in the face of clinical reality and published evidence to the contrary.	We carefully reviewed all eligible ECT studies. We did not identify any Tier 1 ECT studies, as no studies clearly defined the involved population as Tier 1 TRD (as opposed to severe depression, or psychotic depression, or catatonic depression, for example). We did identify 2 Tier 3 ECT vs. sham studies that we had previously not included; these have been added to the review but did not change our findings. Our Tier 1 findings identified a greater negative effect on cognitive functioning of ECT compared to rTMS, although the effect was time-limited and the strength of evidence was low. Clinical experience has suggested that the cognitive effects are more strongly associated with ECT than rTMS. We have now identified the absence of studies addressing the comparison as a limitation of the evidence base.
Mark George	General	The report does not contain the information from the largest TMS depression treatment trial to date. This NIMH-sponsored trial, called OPT-TMS, was published in Spring of 2010.1 It included 199 TRD patients from 4 sites and pioneered a new active sham technique. Some consider it the definitive trial in the area. It is most clearly the largest non-industry sponsored TMS study in depression. It is also the first truly double-blind study of a non-pharmacologic treatment in depression, using the definition of 'double-blind' where no one who knows the randomization status of the patient ever comes in contact with the patient or manipulates the data or data analysis. If this study is not included in the report, the report will be out-of-date and ineffective as soon as it is published. Moreover, several other recent reviews by the American Psychiatric Association and the World Federation of Societies of Biological Psychiatry have included these data in their depression treatment guidelines. Not including this important OPTMS study in this AHRQ review will create a situation where the AHRQ guidelines differ from the other depression treatment guidelines simply because the biggest and best study to date was not included for analysis, even though it was published long	George, et al, 2010 was included during the updated search phase post submission of the Peer Review Draft.

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		before the guidelines were released.	
NIMH	General	This comprehensive review covers nearly three decades of controlled research comparing the efficacy and effectiveness of major nonpharmacologic treatments for depression. The thoroughness and objectivity of the review, including explicit ratings of the strength and quality of the reported trials, constitute the main strength of this document. The major limitation lies in the unevenness of sufficient valid and reliable source data that are required for a definitive assessment and comparison of interventions.	We agree that this is an important limitation, and we now mention it in the section on Limitations in the Evidence Base.
NIMH	General	The report acknowledges that this field of research is in its early stage and therefore the described analyses in some areas might be premature. Further, the reported studies encompass both one of the oldest extant treatments in clinical use for over 70 years [electroconvulsive therapy (ECT)], and newer brain stimulation techniques, such as vagus nerve stimulation (VNS), which has been little studied since its FDA clearance a few years ago. Some reported interventions, including ECT and repetitive transcranial magnetic stimulation (rTMS), have continued to evolve beyond the reported studies, thereby confounding comparisons and meta-analyses with changes in treatment parameters and methodology. While the inclusion of evidence-based psychotherapies [cognitive-behavioral (CBT) and interpersonal (IPT)] adds richness to the review, these interventions are more likely to be used in academic and research settings than in clinical practice and are often overlooked for use in treatment-resistant populations, which is the focus of this review. The gaps in the literature noted in the review result from such comparisons. For example, many of the major ECT efficacy studies were conducted decades ago and despite substantial increases in the benefit:risk ratio of ECT, this treatment is not available in many locales and institutions. In contrast, VNS and rTMS were experimental treatments during most of the years surveyed here, with a resulting inability to study “real-world” depressed patients.	We appreciate the observation and interpretation.
NIMH	General	The review might note that evidence-based psychotherapies for treatment-resistant depression are underrepresented in the comparative efficacy literature for various reasons (e.g., not widely available outside research centers, and both patients and clinicians often view these studies as underpowered or the research protocol too complicated for application in practice settings). Relatedly, trials of somatic treatments and those utilizing psychotherapies commonly	We agree and have made this point in the Limitations of Evidence Base section. Of note, Thase (2007) is included in the current analysis.

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		study separate and distinct patient populations, making comparative-effectiveness conclusions difficult. An example of this issue was the large multisite NIMH *Sequenced Treatment Alternatives to Relieve Depression* (STAR*D) trial. Following an initial trial of the SSRI, citalopram, those patients with incomplete response were offered options for "Level 2" interventions. Less than one-third of eligible patients agreed to be randomized to options that included a cognitive therapy arm. Although the cognitive therapy intervention proved as effective in Level 2 as pharmacotherapy options, data analysis was limited by the unpopularity of this therapy arm. ***Reference:*** Thase ME, Friedman ES, Biggs MM, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: A STAR*D report. *Am J Psychiatry* 2007; 164:739-752.	
NIMH	General	The recent NIMH-funded multisite trial led by Mark George established the efficacy of daily left prefrontal rTMS monotherapy as superior to a highly-sophisticated sham control condition. The George et al. trial also underscores the underappreciated role of the sham condition that is now commonly employed in the control arm of somatic treatment trials. This factor, which many believe has influenced the interpretation of a number of studies, warrants mention in the present review. Because of the need for general anesthesia, "sham ECT" has proven ethically problematic over the years. Given the noninvasive nature of rTMS, there is much objection to the use of a sham control condition, in which the electrode would be placed against the scalp but the magnetic stimulation not applied. The problem is that a completely "inert" sham condition experience has proven not to be credible to patients who are aware of the noise and vibration that typically accompanies active rTMS. This led George et al. to devote much of the first year of their trial to developing a more plausible sham condition, providing the expected sensory experience to the patient without actually administering the magnetic stimulation. Similarly, the limited number of reported vagus nerve stimulation (VNS) studies cited in this review have come under similar criticism for the apparently transparent nature of the control condition. Here, as with the more recent and even more invasive *deep brain stimulation* (DBS), not yet ready for inclusion in the present manuscript, the need for actual surgery makes a true "sham" condition untenable. Rather, investigators have employed a "staggered-start" approach, in which following implantation of the	George, et al, 2010 was included during the update search phase post submission of the Peer Review Draft

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		stimulating "pulse generator" (in the chest, in the case of VNS, with wires leading to electrodes attached to the left vagus nerve in the neck), the device is initially kept "off" -- to be turned "on" at pre-designated times to enable each subject to serve as his or her own control, with "device-off" and subsequent "device-on" ratings obtained (presumably by raters blind to condition). But as with the case of TMS, this approach is dependent on the subjects' remaining "blind" to the treatment condition. Problematically, many individuals are aware of the "on" periods in VNS (typically 30 seconds every 5 minutes), as reflected by changes in voice, hoarseness, or coughing. This remains a methodologic challenge in VNS research, and suggests that blinding of studies performed to date may have been less complete than intended. While this does not change any of the conclusions of the current review, it is worth noting as a potentially significant contributor to the "low strength" of the evidence supporting the antidepressant efficacy of VNS. ***Reference:*** George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: A sham-controlled randomized trial. *Arch Gen Psychiatry* 2010; 67:507-516.	
NIMH	Additional Citation	One "classic" clinical trial from the first generation of the systematic treatment of depression is of such importance and relevance to the present review that it should be included: the 1965 *Medical Research Council* (UK) trial is the only published clinical trial to report true random assignment of depressed patients to ECT or a comparison antidepressant medication arm [in this case either a tricyclic (impramine) or a monoamine oxidase inhibitor (phenelzine)], as well as placebo. This trial provided further evidence for the efficacy of ECT, and helped establish principles of personalized treatment of depression that continue to inform clinical practice. ***Reference:*** Clinical Psychiatry Committee. Clinical trial of the treatment of depressive illness: Report to the Medical Research Council. *Br Med J* 1965; 1:881-886.	We appreciate the reviewer noting this landmark study.. Given its date of publication, it does not meet our search strategy criteria. Further, the group was not a TRD population. Given its import, however, we now acknowledge it in our Appendix H, which identifies important studies not meeting eligibility criteria for our review.
Peer Reviewer #1	Clarity and Usability	While quite lengthy and highly detailed, the report is well structured and well organized with the main points clearly presented. The conclusions can be used to a) identify the gaps in the literature; b) prioritize future research efforts in the area of non-pharmacologic interventions for treatment resistant depression; c) inform policy makers about the funding of these interventions; and d) but does not have sufficient evidence to inform practice decisions. The authors could strengthen their argument by stating the need for more effectiveness trials beyond the available efficacy trials.	Thank you.

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Peer Reviewer #2	Clarity and Usability	The report was well structured. For a long and relatively dense report it was extremely reader friendly and engaging	Thank you.
Peer Reviewer #2	Clarity and Usability	In my opinion the narrative was more clear than the data, again because having six "populations" (and not really knowing how distinct any of them were) which were then combined in various ways, made the data sections feel like a slog at best and overwhelming and confusing at its worst.	See above (same comment)
Peer Reviewer #3	Clarity and Usability	The report is well structured and organized. The main points are clearly presented and the conclusions can be used to inform policy and practice decisions.	Thank you.
Peer Reviewer #4	Clarity and Usability	I would prefer to see the conclusion section of the main report re-state the original questions and provide a one- or two-sentence answer to each in language that typical practicing clinicians would find useful.	By limiting consideration to Tier 1 evidence only, the Strength of Evidence tables in the concluding sections now provide straight forward answers to the key questions.
Peer Reviewer #5	Clarity and Usability	The report is quite lengthy so I doubt few readers will read it in toto. On the other hand, the tables are quite useful in allowing the reader to quickly identify key findings	We appreciate the observation.
Peer Reviewer #5	Clarity and Usability	The report does a surprisingly good job of trying to get its hands around a complex area. The authors are well organized and generally clear in their approach (except as previously noted).	Thank you.
Peer Reviewer #6	Clarity and Usability	Excellent report well designed, well organized, well written, clear, and important to the field.	Thank you.
Peer Reviewer #7	Clarity and Usability	The report is well structured and organized. The main points are clearly presented. Despite the paucity of good studies, the conclusions can be used to inform policy and/or practice decisions.	Thank you.
Peer Reviewer #8	Clarity and Usability	Thank you for the opportunity to review this document. It is very well done and of high quality.	Thank you.
Peer Reviewer #9	Clarity and Usability	the report is well organized and proably as clear as can be given the level of evidence. the main points are clear enough, especially in the overview. I am afraid that the conclusions will not be very useful for policy or practice decisions given the current state of CER for TRD. Perhaps its greatest contribution will be to the research community and research-funding community.	We appreciate the observation. We hope that this CER will prove useful to all decision makers.
Peer Reviewer #11	Clarity and Usability	It is well organized, but may be a bit difficult to use considering the vast quantity of information presented.	Thank you.

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Bryan Olin, Cyberonics		Bajbouj, M., A. Merkl, et al. (2010). "Two-year outcome of vagus nerve stimulation in treatment-resistant depression." Journal of Clinical Psychopharmacology 30(3): 273-281. George, M. S., A. J. Rush, et al. (2005). "A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression." Biol Psychiatry 58(5): 364-73. Nahas, Z., L. B. Marangell, et al. (2005). "Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes." J Clin Psychiatry 66(9): 1097-104. Rush, A. J., L. B. Marangell, et al. (2005). "Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial." Biological Psychiatry 58(5): 347-354. Sackeim, H. A., S. K. Brannan, et al. (2007). "Durability of antidepressant response to vagus nerve stimulation (VNS)." Int J Neuropsychopharmacol 10(6): 817-26.	Bajbouj (2010) This reference was excluded for the present analysis due to a lack of comparison of interventions. The study analyzes outcome measures after 3, 12, and 24 months of vagal nerve stimulation George (2005) This study was excluded from Key Question 2 (maintenance of response) analysis due to wrong study design (observational study). The protocol for this review states that only randomized controlled trials and meta-analyses are eligible study designs for this key question. Nahas (2005)This article was excluded from this review due to no comparison. This study analyzes the outcomes from patients treated with vagal nerve stimulation. No other intervention is compared. Rush (2005) This study is included in the current analysis. Sackeim (2007) This study was not included in the current analysis because it does not contain a comparison of interest. The study analyzes outcomes after vagal nerve stimulation and compares outcomes between responders and non-responders.
Bryan Olin, Cyberonics		Updated Practice Guidelines for the Treatment of Patients with Major Depressive Disorder from the APA	APA Guidelines - This reference is a set of guidelines. Guidelines do not fit the inclusion criteria for appropriate publication types. The guidelines were not included in the analysis of this review.
Bryan Olin, Cyberonics		Reference to clinical trial NCT00305565 at Clinicaltrials.gov	This would not meet criterion for inclusion, wrong comparison