

# ***AHRQ Systematic Review Surveillance Program***

**CER #33:** Nonpharmacologic Interventions for Treatment Resistant Depression in Adults

**Original Release Date:** September 2011

**Surveillance Report:** August 2012

**Surveillance Report:** April 2016

## **Summary of Key Findings from Surveillance Report:**

- Key Question 1a: Conclusions related to psychotherapy may not be current due to no Tier 1 studies identified in the original review, and an identified study which found Mindfulness Based Cognitive Therapy (MBCT) as an adjunct to be associated better outcomes than Health Enhancement Program (HEP). All other conclusions are likely current.
- Key Question 1b: The conclusions in the original systematic review are likely current.
- Key Question 2: The conclusions in the original systematic review are likely current. However, we identified a Tier 3 study comparing electroconvulsive therapy (ECT) to cognitive behavior therapy (CBT) and antidepressants, which found that CBT was more effective than ECT or antidepressants alone for sustained response and longer relapse free times.
- Key Question 3: The conclusions in the original systematic review are likely current.
- Key Question 4: The conclusions in the original systematic review are likely current.

- Key Question 5: Conclusions related to psychotherapy may not be current due to no Tier 1 studies identified in the original review, and an identified study which found when comparing MBCT to HEP as an adjunct, personality disorder and anxiety were related to poorer outcomes, with no difference associated with other demographic and medical variables. All other conclusions are likely current.
- Key Question 6: Conclusions related to psychotherapy may not be current due to no Tier 1 studies identified in the original review, and an identified study which found MBCT to be associated better outcomes than HEP at 8 weeks. Both MBCT and HEP as an adjunct were associated with improvement on the Clinical Global Impressions (CGI) scale at 8 and 52 weeks. All other conclusions are likely current.

**Signal Assessment:** The signals examined in this surveillance assessment suggest that portions of the original systematic review may not be current.

**Authors:**

Karli Kondo  
Kara Winchell

**Conflict of Interest:**

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

**Acknowledgements:**

The authors gratefully acknowledge the following individuals for their contributions to this project: Robin Paynter and Rose Relevo for conducting searches.

## **Reviewers**

Eric Plakun, M.D.  
Psychiatrist  
Austin Riggs Center  
Stockbridge, MA

Stuart Eisendrath, M.D.  
Professor of Clinical Psychiatry  
Director of Clinical Services  
Director of Depression Center at Langley Porter  
University of California San Francisco  
San Francisco, CA

## Table of Contents

Introduction.....	1
Methods.....	2
Prior Surveillance.....	2
Literature Searches .....	2
Study Selection .....	2
Expert Opinion .....	2
FDA Class I Device Recalls and Withdrawals .....	3
Check for Qualitative Signals.....	3
Signal Assessment for Currency of the Systematic Review .....	4
Results .....	4
Prior Surveillance.....	4
Literature Search .....	4
FDA Black Box Warnings (or Class I Device Recalls and Withdrawals) .....	4
Expert Opinion .....	4
Identifying Qualitative Signals.....	5
Signal Assessment .....	6
References .....	8
Appendices.....	9
Appendix A. Search Strategy.....	A-1
Appendix B. Inclusion and Exclusion Criteria from Original Systematic Review .....	B-1
Appendix C. Literature Search Results.....	C-1
Appendix D. Questionnaire Sent to Expert Reviewers .....	D-1
Abstracts from Relevant Literature/References .....	D-5
Appendix E. Summary Tables* .....	E-1
References .....	E-9

# Introduction

The purpose of the surveillance process for the EPC Program is to determine whether the conclusions of a systematic review are current. The surveillance process examines the conclusions to the key questions as written, and does not evaluate the currency of the original scope (i.e., key questions, included interventions). A limited number of systematic reviews are selected for surveillance annually based on popularity, use in obtaining continuing medical education certificates, potential impact for changing the field, and use in clinical practice guidelines.

Comparative Effectiveness Review (CER) #3, titled *Nonpharmacologic Interventions for Treatment Resistant Depression in Adults*, was originally released in September 2011.<sup>1</sup>

The key questions for the original systematic review are as follows:

**Key Question 1a.** For adults with treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic [i.e., pharmacologic] intervention), do non-pharmacologic interventions such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), or demonstrated effective psychotherapy (e.g., cognitive therapy [CBT or interpersonal therapy [IPT]]) differ in efficacy or effectiveness in treating acute phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?

**Key Question 1b.** How do these nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms after two or more failed adequate trials?

**Key Question 2.** For adults with TRD, do nonpharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence) whether as a single treatment or part of a combination treatment?

**Key Question 3.** Do nonpharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic [frozen or hyper] or psychotic symptoms)?

**Key Question 4.** For adults with TRD, do nonpharmacologic interventions differ in their safety, adverse events, or adherence? Adverse effects of interest include but are not limited to amnesia, memory loss, headaches, and postoperative complications.

**Key Question 5.** How do the efficacy, effectiveness, or harms of treatment with nonpharmacologic treatments for TRD differ for the following subpopulations: elderly, very elderly, and other demographic groups (defined by age, ethnic or racial groups, and sex); and patients with medical comorbidities (e.g., seizure history, stroke, diabetes, dementia, perinatal depression, ischemic heart disease, cancer).

**Key Question 6.** For adults with TRD, do non-pharmacologic interventions differ in regard to other health-related outcomes (e.g., quality of life)?

Our surveillance assessment began in March, 2016. We conducted an electronic search for literature published since the end date of the most recent surveillance report search date. After

completing a scan of this literature to identify evidence potentially related to the key questions in this systematic review, we contacted experts involved in the original systematic review to request their opinions as to whether the conclusions had changed.

## **Methods**

### **Prior Surveillance**

A surveillance report for the original systematic review was released in August, 2012, and included a search for relevant literature published between January 2010 and March 2012, expert opinion, and a search of U.S. Food and Drug Administration (FDA), Health Canada, and Medicines and Healthcare Products Regulatory Agency (MHRA) surveillance alerts received from the Emergency Care Research Institute (ECRI). The findings from this report are included in our assessment.<sup>2</sup>

### **Literature Searches**

We conducted a literature search of PubMed covering March 2012 to March 2016, using the identical search strategy used for the original review and searching for studies published since the end date of the most recent surveillance search.<sup>2</sup>

The search was conducted to assess the currency of conclusions using journals from among the top 10 journals from relevant specialty subject areas and among those most highly represented among the references for the original review. We included the journals searched in the previous surveillance assessment. The included journals were five high-profile general medical interest journals (Annals of Internal Medicine, The BMJ, JAMA, Lancet, and the New England Journal of Medicine) and five specialty journals (American Journal of Psychiatry, Archives of General Psychiatry, Biological Psychiatry, British Journal of Psychiatry, and Journal of Clinical Psychiatry). The search strategy is reported in Appendix A.

### **Study Selection**

Using the same inclusion and exclusion criteria as the original systematic review (see Appendix B), one investigator reviewed the titles and abstracts of the 10 high-impact journal search results (Appendix C). We included systematic reviews and meta-analyses, whether or not they were included (as a study design) in the original systematic review. For systematic reviews and meta-analyses, we considered findings only if all included studies met criteria that a) all studies were not included or excluded from the original systematic review, b) all studies were not included in a prior surveillance report (if applicable), and c) all studies met inclusion criteria for the original systematic review. Reviews for which one or more study did not meet our criteria were used to identify potentially relevant primary research. Reviews of systematic reviews were not included.

### **Expert Opinion**

We shared the conclusions of the original systematic review and most recent surveillance assessment, findings from the literature analysis, and the newly identified studies with fourteen experts in the field (seven original peer reviewers and seven technical expert panel [TEP] members) to request their assessment of the currency of the original review conclusions and

their recommendations of any relevant new studies. Two subject matter experts responded to our request. Appendix D shows the form experts were asked to complete.

## **FDA Class I Device Recalls and Withdrawals**

We searched the FDA MedWatch online database website for class I recalls and device withdrawals relevant to the key questions in this systematic review.

## **Check for Qualitative Signals**

The authors of the original systematic review conducted qualitative synthesis of data examining the effectiveness of non-pharmacological interventions for treatment resistant depression (active and maintenance), including a comparison to pharmacological interventions, harms, and differences by clinical, demographic, and comorbid condition subpopulations. The review classified studies into three tiers. The primary focus of the original review were individuals who had two or more known pharmacologic treatment failures (Tier 1), and studies including participants meeting this criterion were considered in the rating of the strength of evidence (SOE). The review also included studies in which participants had one or more known treatment failures (Tier 2), as well as studies for which the number of treatment failures were not specified, but that the population was likely to have had two or more pharmacologic treatment failures. This group also included individuals referred to electroconvulsive therapy (ECT; Tier 3). Tiers 2 and 3 were not considered in the review's SOE ratings; however, results were summarized. We compared the conclusions of the included abstracts to the conclusions of the original systematic review and surveillance report(s), and assessed expert input, and FDA alert information to identify qualitative signals about the currency of conclusions.

## **Compilation of Findings and Conclusions**

For this assessment we constructed a summary table (Appendix E) that includes the key questions and conclusions from the original systematic review, findings of the new literature search, *Class I recalls and withdrawals*, and the expert assessments that pertained to each key question. Because we did not find any FDA Class I recalls or withdrawals relevant to the key questions in this systematic review, we did not include a column for this in the summary table. We categorized the currency of conclusions using a 3-category scheme:

- Original conclusion is still valid and this portion of the systematic review is likely current
- Original conclusion is possibly out of date and this portion of the systematic review may not be current
- Original conclusion is out of date.

We considered the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the systematic review conclusion as still valid, we classified the systematic review conclusion as likely current.
- If we found some new evidence that might change the systematic review conclusion, and/or a minority of responding experts assessed the systematic review conclusion as having new evidence that might change the conclusion, then we classified the systematic review conclusion as possibly not current.



- If we found new evidence that rendered the systematic review conclusion out of date or no longer applicable, we classified the systematic review conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

## Signal Assessment for Currency of the Systematic Review

We used the following considerations in our assessment of currency of the systematic review:

- **Strong signal:** A report is considered to have a strong signal if new evidence is identified that clearly renders conclusions from the original systematic review out of date, such as the addition or removal of a drug or device from the market or a new FDA boxed warning.
- **Medium signal:** A report is considered to have a medium signal when new evidence is identified which may change the conclusions from the original systematic review. This may occur when abstract review and expert assessment indicates that some conclusions from the original systematic review may not be current, or when it is unclear from abstract review how new evidence may impact the findings from the original systematic review.
- **Weak signal:** A report is considered to have a weak signal if no new evidence is identified that would change the conclusions from the original systematic review. This may occur when no new evidence is identified, or when some new evidence is identified but it is clear from abstract review and expert assessment that the new evidence is unlikely to change the conclusions of the original systematic review.

## Results

### Prior Surveillance

Prior surveillance of the topic included 9 studies and consultation with 5 subject matter experts, and concluded that all conclusions related to comparative efficacy and safety were current. The assessment did not include additional safety concerns, and while several identified studies suggested the efficacy of TMS, VNS, and some types of Cognitive Behavioral Therapy (CBT), sample sizes were small and studies were not controlled.<sup>2</sup>

### Literature Search

The literature search identified 10 unique titles from the 10 selected high profile general medical and specialty journals (Appendix C). Upon abstract review, seven studies were rejected because they did not meet the original systematic review inclusion criteria (see Appendix B). The remaining 3 studies<sup>3-5</sup> were examined for potential to change the results of the original systematic review.

### FDA Class I Device Recalls and Withdrawals

We did not find any FDA class I device recalls or withdrawals relevant to the key questions in this systematic review.

### Expert Opinion

We shared the conclusions of the original review with fourteen experts in the field (seven original peer reviewers and seven TEP members) to request their assessment of the currency of report conclusions and their recommendations of any relevant new studies. Two subject matter experts responded.

One expert did not comment specifically on the currency of the conclusions in the original systematic review; however, identified a potentially relevant study related to Key Question 1a, 5, and 6.<sup>6</sup> The second expert identified two studies for Key Questions 1a, 2, and 6.<sup>7,8</sup> One study,<sup>7</sup> was excluded because it examined psychoanalytic therapy, which was not an intervention of interest in the original systematic review. The second study,<sup>8</sup> was excluded because participants did not meet the criteria for “treatment resistant,” defined in the original systematic review (see [methods] Check for Qualitative Signals section above). The second expert believed conclusions related to Key Questions 1a and 2 to be current and stated “no data” for all others (see Appendix E).

## Identifying Qualitative Signals

Appendix E shows the original key questions, the conclusions of the original systematic review and prior surveillance assessment, expert opinion, and the assessment of the currency of the systematic review.

For Key Question 1a, which examined the effectiveness of non-pharmacological interventions for acute phase depressive symptoms, conclusions related to psychotherapy may no longer be current. The original review did not identify any Tier 1 studies (thus did not form conclusions/rate SOE). One (Tier 1) RCT, identified by an expert, found Mindfulness Based Cognitive Therapy (MBCT) to be associated with a greater reduction in depression severity and significantly more responders than Health Enhancement Program (HEP).<sup>6</sup> All other conclusions are likely current.

For Key Question 1b, which compared the effectiveness of non-pharmacological to pharmacological interventions, the original systematic review conclusion that ECT resulted in a larger response rate than pharmacotherapy is likely current. Congruent with the original review, we identified one (Tier 1) RCT comparing ECT to algorithm-based pharmacological treatment (APT) for bipolar disorder that reported a larger response rate, and greater symptom reduction associated with ECT.<sup>4</sup> All other conclusions are likely current.

For Key Question 2, examining the efficacy of non-pharmacological interventions for maintenance, the conclusions in the original systematic review are likely current. However, we identified a Tier 3 study comparing ECT to CBT augmentation, and antidepressants alone, which found that CBT was more effective than ECT or antidepressants alone for sustained response and longer relapse free times.<sup>3</sup> No studies in the original review compared CBT to ECT.

We identified no studies for Key Question 3, and the prior surveillance assessment concluded that the original review conclusions were likely current.

For Key Question 4, examining harms and adherence, the original systematic review found mixed evidence related to the effect of ECT on cognitive functioning (insufficient evidence); this finding is likely current. The August 2012 surveillance assessment included one study that found greater impairments in verbal memory associated with higher and moderate intensity versus low intensity ECT.<sup>2</sup> We identified two Tier 3 studies that found no changes in cognitive functioning associated with ECT.<sup>3,5</sup> In addition, no Tier 1 studies in the original review examined adherence

associated with psychotherapy (no conclusion/SOE). One small Tier 1 RCT (n=131), identified by an expert found no difference in adherence when comparing MBCT to HEP.<sup>6</sup> All other conclusions are likely current.

For Key Question 5, examining subpopulations, the conclusions related to psychotherapy may no longer be current. The original systematic review identified no Tier 1 studies that examined differential effects in subpopulations associated with psychotherapy (no conclusion/SOE). One RCT, identified by an expert found that when comparing MBCT to HEP, the presence of a personality disorder or comorbid anxiety disorder was related to poorer outcomes. There was no difference associated with gender, sociodemographic group, education, or medical comorbidity.<sup>6</sup> All other conclusions are likely current.

For Key Question 6, which examined other health related outcomes, the original systematic review conclusions related to psychotherapy may no longer be current. The original review identified no Tier 1 studies examining the effect of psychotherapy on other outcomes. One RCT, identified by a reviewer found that while both MBCT and HEP were effective in improving CGI scores from baseline (at both 8 and 52 weeks), at 8 weeks, participants in the MBCT group experienced greater improvement overall, as well as greater reductions in symptom severity. There were no significant differences between groups at 52 weeks.<sup>6</sup> All other conclusions are likely current.

## **Signal Assessment**

The SRC conclusions based on the results of the prior surveillance assessment, literature published since the original report, FDA class I device recalls and withdrawals, and expert assessment is that:

- Key Question 1a: Conclusions related to psychotherapy may not be current due to no Tier 1 studies identified in the original review, and an identified study which found Mindfulness Based Cognitive Therapy (MBCT) as an adjunct to be associated better outcomes than Health Enhancement Program (HEP). All other conclusions are likely current.
- Key Question 1b: The conclusions in the original systematic review are likely current.
- Key Question 2: The conclusions in the original systematic review are likely current. However, we identified a Tier 3 study comparing ECT to CBT and antidepressants, which found that CBT was more effective than ECT or antidepressants alone for sustained response and longer relapse free times.
- Key Question 3: The conclusions in the original systematic review are likely current.
- Key Question 4: The conclusions in the original systematic review are likely current.
- Key Question 5: Conclusions related to psychotherapy may not be current due to no Tier 1 studies identified in the original review, and an identified study which found when comparing MBCT to HEP as an adjunct, personality disorder and anxiety were related to poorer outcomes, with no difference associated with other demographic and medical variables. All other conclusions are likely current.
- Key Question 6: Conclusions related to psychotherapy may not be current due to no Tier 1 studies identified in the original review, and an identified study which found MBCT to be associated better outcomes than HEP at 8 weeks. Both MBCT and HEP as an adjunct were associated with improvement on the CGI at 8 and 52 weeks. All other conclusions are likely current.

The signal for this report is medium suggesting that the some of the conclusions in the original systematic review are may not be current.

## References

1. Gaynes BN, Lux LJ, Lloyd SW, et al. AHRQ Comparative Effectiveness Reviews. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011.
2. Newberry S, Chafen JS, Maglione M, Motala A, Larkin J, Shekelle P. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. AHRQ Comparative Effectiveness Review Surveillance Program. 2012.
3. Brakemeier EL, Merkl A, Wilbertz G, et al. Cognitive-behavioral therapy as continuation treatment to sustain response after electroconvulsive therapy in depression: a randomized controlled trial. *Biological psychiatry*. Aug 1 2014;76(3):194-202.
4. Schoeyen HK, Kessler U, Andreassen OA, et al. Treatment-resistant bipolar depression: a randomized controlled trial of electroconvulsive therapy versus algorithm-based pharmacological treatment. *The American journal of psychiatry*. Jan 2015;172(1):41-51.
5. Spaans HP, Verwijk E, Comijs HC, et al. Efficacy and cognitive side effects after brief pulse and ultrabrief pulse right unilateral electroconvulsive therapy for major depression: a randomized, double-blind, controlled study. *The Journal of clinical psychiatry*. Nov 2013;74(11):e1029-1036.
6. Eisendrath SJ, Gillung E, Delucchi KL, et al. A Randomized Controlled Trial of Mindfulness-Based Cognitive Therapy for Treatment-Resistant Depression. *Psychotherapy and psychosomatics*. 2016;85(2):99-110.
7. Fonagy P, Rost F, Carlyle JA, et al. Pragmatic randomized controlled trial of long-term psychoanalytic psychotherapy for treatment-resistant depression: the Tavistock Adult Depression Study (TADS). *World Psychiatry*. 2015;14:10.
8. Wiles NJ, Thomas L, Turner N, et al. Long-term effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: follow-up of the CoBaIT randomised controlled trial. *The Lancet Psychiatry*. 2016;3(2):137-144.
9. Brakemeier EL, Radtke M, Engel V, et al. Overcoming treatment resistance in chronic depression: a pilot study on outcome and feasibility of the cognitive behavioral analysis system of psychotherapy as an inpatient treatment program. *Psychotherapy and psychosomatics*. 2015;84(1):51-56.

# **Appendices**

**Appendix A: Search Strategy**

**Appendix B: Inclusion and Exclusion Criteria from Original Systematic Review**

**Appendix C: Literature Search Results**

**Appendix D: Questionnaire Sent to Expert Reviewers**

**Appendix E: Summary Table**

## Appendix A. Search Strategy

Surveillance Search for Treatment Resistant Depression

Searched on March 25, 2016

PubMed/Medline

Original Search	<pre> ((((("Vagus Nerve Stimulation"[Mesh]) OR "vagus nerve stimulation"[Text Word])) AND (((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) NOT ((((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND ( ( Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] ) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) OR (((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) AND "Case-Control Studies"[Mesh]))) OR (((("Transcranial Magnetic Stimulation"[Mesh] OR "(r)tms"[Text Word])) AND (((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) NOT (((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND ( ( Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] ) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) OR ((((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) AND "Case-Control Studies"[Mesh]))) OR (((((((("Longitudinal Studies"[Mesh] OR "Comparative Study" [Publication Type] OR "Cohort Studies"[Mesh]) OR "observational studies"[Text Word])) AND (((((((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) NOT ((((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND ( ( Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] ) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) OR (((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) AND "Case-Control Studies"[Mesh]))) AND ((electroconvulsive therapy[mesh] OR ect[tw] OR "electroconvulsive therapy"[tw]))) OR (((("Randomized Controlled Trial" [Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR "Random Allocation"[Mesh])) AND (((((((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) NOT (((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND ( ( Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] ) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) OR (((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) AND "Case-Control Studies"[Mesh]))) AND ((electroconvulsive therapy[mesh] OR ect[tw] OR "electroconvulsive therapy"[tw]))) OR ((((((socioenvironmental therapy[mesh] OR "interpersonal psychotherapy"[tw] OR ipt[tw] OR psychotherapy[mesh] OR cognitive therapy[mesh] OR "cognitive behavioral therapy"[tw] OR cbt[tw])) AND (((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) NOT (((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND ( ( Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] ) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) OR ((((("Depression"[Mesh] OR "Depressive Disorder"[Mesh]) AND Humans[Mesh] AND English[lang] AND adult[MeSH])) AND "Case-Control Studies"[Mesh]))) AND ((drug resistance[mesh] OR refractory[tw] OR resistant[tw])) </pre>
Date Limits	<pre> AND ("2012/03/20"[Date - Entrez] : "3000"[Date - Entrez]) </pre>
N=204	
Journal Limits	<pre> AND ((((("Annals of internal medicine"[Journal]) OR "British medical journal"[Journal]) </pre>

	OR "JAMA"[Journal]) OR "The New England journal of medicine"[Journal])) OR (((("The American journal of psychiatry"[Journal]) OR "Archives of general psychiatry"[Journal]) OR "Biological psychiatry"[Journal]) OR "The British journal of psychiatry : the journal of mental science"[Journal]) OR "The Journal of clinical psychiatry"[Journal])
N=10	



## Appendix B. Inclusion and Exclusion Criteria from Original Systematic Review

To summarize, interventions included for one or more of the key questions (KQs) are:

- Nonpharmacologic therapies, for KQs 1–6:
  - ECT
  - rTMS
  - VNS
  - Evidence-based psychotherapy, specifically cognitive therapy (CBT or IPT)
- Pharmacologic, for KQ 1b only, at least one of the antidepressants listed below:
  - Selective serotonin reuptake inhibitors (SSRIs): citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
  - Serotonin-norepinephrine reuptake inhibitors: desvenlafaxine, duloxetine, mirtazapine, venlafaxine
  - Serotonin modulators: nefazodone and trazodone
  - Tetracyclic: mirtazapine
  - Other antidepressants: bupropion
  - Tricyclic antidepressants: amitriptyline, clomipramine, desipramine, doxepin, imipramine, maprotiline, mianserin, nortriptyline
  - Monoamine oxidase inhibitors (MAOIs): phenelzine, tranylcypromine
  - Augmentation strategies with methylphenidate; T4/cytomel; liothyronine; buspirone; lithium or amilsupride; aripiprazole; olanzapine; quetiapine; risperidone; ziprasidone.

For each KQ, we specified inclusion and exclusion criteria for studies and specified the outcome measures of interest (Table 2). For efficacy and effectiveness (all KQs except KQ 4), we first focused on head-to-head RCTs comparing one intervention with another. This body of work provides direct evidence about the comparisons. When sufficient head-to-head evidence was unavailable, we evaluated placebo- or sham-controlled evidence; in some cases, studies might have used “treatment as usual” as the control arm. In any of these cases, the evidence provides only indirect evidence. Systematic evidence reviews or meta-analyses based on a systematic literature search were eligible for inclusion for each KQ. For reviewing adverse events (KQ 4), per our standard approach, we include observational studies. Finally, given the dearth of randomized controlled data that our preliminary review suggested was available for KQ 3 on psychiatric subtypes, KQ 5 on subgroups, and KQ 6 on quality of life, for these KQs we included observational studies (limited to prospective and retrospective cohort studies and case control studies). We do not formally distinguish efficacy from effectiveness trials.

## Appendix C. Literature Search Results

1. Brakemeier EL, Merkl A, Wilbertz G, et al. Cognitive-behavioral therapy as continuation treatment to sustain response after electroconvulsive therapy in depression: a randomized controlled trial. *Biological psychiatry*. Aug 1 2014;76(3):194-202.
2. Downar J, Geraci J, Salomons TV, et al. Anhedonia and reward-circuit connectivity distinguish nonresponders from responders to dorsomedial prefrontal repetitive transcranial magnetic stimulation in major depression. *Biological psychiatry*. Aug 1 2014;76(3):176-185.
3. Dunner DL, Aaronson ST, Sackeim HA, et al. A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: durability of benefit over a 1-year follow-up period. *The Journal of clinical psychiatry*. Dec 2014;75(12):1394-1401.
4. Fox MD, Buckner RL, White MP, Greicius MD, Pascual-Leone A. Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. *Biological psychiatry*. Oct 1 2012;72(7):595-603.
5. Hollinghurst S, Carroll FE, Abel A, et al. Cost-effectiveness of cognitive-behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: economic evaluation of the CoBaT Trial. *The British journal of psychiatry: the journal of mental science*. Jan 2014;204(1):69-76.
6. Kessler U, Schoeyen HK, Andreassen OA, et al. The effect of electroconvulsive therapy on neurocognitive function in treatment-resistant bipolar disorder depression. *The Journal of clinical psychiatry*. Nov 2014;75(11):e1306-1313.
7. Liston C, Chen AC, Zebley BD, et al. Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biological psychiatry*. Oct 1 2014;76(7):517-526.
8. Schoeyen HK, Kessler U, Andreassen OA, et al. Treatment-resistant bipolar depression: a randomized controlled trial of electroconvulsive therapy versus algorithm-based pharmacological treatment. *The American journal of psychiatry*. Jan 2015;172(1):41-51.
9. Spaans HP, Sienaert P, Bouckaert F, et al. Speed of remission in elderly patients with depression: electroconvulsive therapy v. medication. *The British journal of psychiatry: the journal of mental science*. Jan 2015;206(1):67-71.
10. Spaans HP, Verwijk E, Comijs HC, et al. Efficacy and cognitive side effects after brief pulse and ultrabrief pulse right unilateral electroconvulsive therapy for major depression: a randomized, double-blind, controlled study. *The Journal of clinical psychiatry*. Nov 2013;74(11):e1029-1036.

## Appendix D. Questionnaire Sent to Expert Reviewers

# ***AHRQ Systematic Review Surveillance Program***

## **Reviewer Form**

**Title of Original Systematic Review:** Nonpharmacologic Interventions for Treatment Resistant Depression in Adults

[Link to Report](#)

**Prior Surveillance:** August 2012

[Link to Surveillance Report](#)

**Name of Reviewer:** \_\_\_\_\_

### **Instructions:**

The AHRQ Scientific Resource Center (SRC) periodically conducts surveillance of published AHRQ systematic reviews to assess the currency of review conclusions. The goal of this process is to identify signals that a report may be out of date. One part of this process includes soliciting expert review of our synthesis of recently published literature and previous surveillance assessments.

The original systematic review was published in September 2011. The original systematic review search dates went through November 2010. Previous surveillance was conducted on August 2012, with the search extending through March 2012. We conducted a bridged literature search of select high impact journals from March 2012 to March 2016 and identified evidence potentially related to the key questions of the original systematic review.

The table below highlights the conclusions from the original systematic review, the findings and assessment of the prior surveillance assessment, and a summary of the relevant recently published literature. No FDA Class I recalls related to non-pharmacological treatments for depression were identified. Abstracts from relevant literature are included at the end of the document. If you would like a list of our full search results, please let us know.

Please review the table and provide responses to the questions for each key question below. The primary goal of this review is to identify any important new studies, drugs, interventions, or devices you know of that we may have missed in our literature search and to understand if any new evidence exists which may alter the conclusions of the original systematic review.

## Key Question 1a:

For adults with treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic [i.e., pharmacologic] intervention), do non-pharmacologic interventions such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), or demonstrated effective psychotherapy (e.g., cognitive therapy [CBT or IPT]) differ in efficacy or effectiveness in treating acute phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?

### Prior Surveillance Assessment (August 2012):

- Likely current
  - The prior surveillance identified three studies – two very small new uncontrolled trials report positive effects of rTMS on patients with TRD, and one small study of three different intensity levels of ECT found no differences in efficacy between the two higher intensities but a lower effect on the BDI score with the lowest intensity.

### Current Literature Analysis:

- We identified a RCT comparing unilateral brief pulse to ultra-brief pulse ECT for clinical depression. Significantly more receiving brief pulse achieved remission and the brief pulse group achieved remission in significantly fewer sessions.

### Reviewer Questions:

1. "Are the original report conclusions still supported by the current evidence?"

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

## Key Question 1b:

How do these nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms after two or more failed adequate trials?

### Prior Surveillance Assessment (August 2012):

- Likely Current
  - The prior surveillance identified three studies. One found greater symptom reduction associated with augmentation of pharmacological treatment with High Frequency Repetitive Transcranial Magnetic Stimulation (HFrTMS) as compared to pharmacological treatment alone. The second found that TMS with no cognitive emotional reactivation and positive reactivation were associated with improvement on the BDI. No improvement was associated with TMS with negative cognitive reactivation. The third study found that VNS implants as an adjunct to pharmacotherapy was associated with improvement on the BDI but not other measures.

### Current Literature Analysis:

- We identified a small multi-site RCT comparing ECT to algorithm-based pharmacological treatment (APT) in for the treatment of resistant bipolar disorder. Results indicated that ECT was significantly more effective than APT for symptom reduction, and that response rates were significantly higher for participants receiving ECT.

#### **Reviewer Questions:**

1. "Are the original report conclusions still supported by the current evidence?"

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

#### **Key Question 2:**

For adults with TRD, do nonpharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence) whether as a single treatment or part of a combination treatment?

#### **Prior Surveillance Assessment (August 2012):**

- Likely Current
  - The prior surveillance identified one small study that found rumination-focused Cognitive Behavioral Therapy (CBT) to improve remission better than treatment as usual.

#### **Current Literature Analysis:**

- We identified a small phase II RCT examining individuals with MDD who had responded to ECT that compared continuation treatment with ECT to CBT and antidepressants. Results indicated that a significantly higher proportion of participants receiving CBT sustained response as compared to both ECT and antidepressants. Participants receiving CBT experienced significantly longer relapse-free times as compared to both ECT and antidepressants (over 12-months).<sup>9</sup>

#### **Reviewer Questions:**

1. "Are the original report conclusions still supported by the current evidence?"

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

#### **Key Question 3:**

Do nonpharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic [frozen or hyper] or psychotic symptoms)?

#### **Prior Surveillance Assessment (August 2012):**

- Likely Current

- The prior surveillance assessment identified one small trial of ultra-brief ECT and found no difference in response in participants with unipolar as compared to bipolar depression.

#### **Current Literature Analysis:**

- No studies were identified.

#### **Reviewer Questions:**

1. "Are the original report conclusions still supported by the current evidence?"

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

### **Key Question 4:**

For adults with TRD, do nonpharmacologic interventions differ in their safety, adverse events, or adherence? Adverse effects of interest include but are not limited to amnesia, memory loss, headaches, and postoperative complications.

#### **Prior Surveillance Assessment (August 2012):**

- Likely Current
  - TMS: The prior surveillance identified five small studies that identified a range of adverse events – headache, scalp pain, dizziness, a combination of a foul taste and smell sensation, seizures in a patient with a history of seizures, and suicidal ideation in patients with history of suicidal ideation.
  - ECT was associated with greater impairments in verbal memory associated with higher intensity therapy.
  - VNS was associated with no serious AEs but commonly with hoarseness, dyspnea, nausea, pain, and anxiety; less frequent were cough, chest tightness, sore throat, dysphagia, and earache.

#### **Current Literature Analysis:**

- ECT: We identified two small studies that found no difference in cognitive functioning as compared to CBT and antidepressants,<sup>9</sup> or between unilateral brief pulse and ultra-brief pulse ECT.<sup>5</sup>

#### **Reviewer Questions:**

1. "Are the original report conclusions still supported by the current evidence?"

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

### **Key Question 5:**

How do the efficacy, effectiveness, or harms of treatment with nonpharmacologic treatments for TRD differ for the following subpopulations: elderly, very elderly, and other demographic groups

(defined by age, ethnic or racial groups, and sex); and patients with medical comorbidities (e.g., seizure history, stroke, diabetes, dementia, perinatal depression, ischemic heart disease, cancer).

**Prior Surveillance Assessment (August, 2012):**

- Likely Current
  - The prior surveillance identified a relatively small study of ECT among elderly with varying degrees of cognitive impairment that found that those with no or mild cognitive impairment experienced significant improvement in depressive symptoms. Older adults with dementia experienced non-significant improvement.

**Current Literature Analysis:**

- No studies were identified

**Reviewer Questions:**

1. "Are the original report conclusions still supported by the current evidence?"

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

**Key Question 6:**

For adults with TRD, do non-pharmacologic interventions differ in regard to other health-related outcomes (e.g., quality of life)?

**Prior Surveillance Assessment (August 2012):**

- Likely Current
  - The prior surveillance identified a very small study that found increased QOL scores for global, physical, and psychological domains but not social or environmental associated with of HFrTMS.

**Current Literature Analysis:**

- No studies were identified

**Reviewer Questions:**

1. "Are the original report conclusions still supported by the current evidence?"

[Click here to enter text.](#)

2. Are there any published or unpublished studies that you know of that we may have overlooked?

[Click here to enter text.](#)

## Original Systematic Review Conclusions and Literature Analysis

**Title of Original Systematic Review:** Nonpharmacologic Interventions for Treatment Resistant Depression in Adults

**Original Systematic Review Published:** September 2011

**Original Systematic Review Search Dates:** 1980 to November 2010

**(Most Recent) Surveillance Report Published:** August 2012

**(Most Recent) Surveillance Report Search Dates:** January 2010 to March 2012

**Current Literature Search Dates:** March 2012 to March 2016

The conclusions from the original systematic review, findings and assessment of the prior surveillance assessment, and a summary of the relevant recently published literature. No FDA Class I recalls were identified. Abstracts are provided at the end of the document.

Table 1. Key Question 1a: For adults with treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic [i.e., pharmacologic] intervention), do non-pharmacologic interventions such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), or demonstrated effective psychotherapy (e.g., cognitive therapy[CBT or IPT]) differ in efficacy or effectiveness in treating acute phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?

Conclusions from Original Systematic Review <a href="#">Link to Report</a>	Findings and Assessment from prior Surveillance Assessment (August 2012) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
A very small number of head-to-head trials have shown no differences between ECT and rTMS or ECT and ECT+rTMS for depressive severity, response rates, and remission rates. No trial involved a direct comparison of psychotherapy with another non-pharmacologic intervention.	<u>Likely Current</u>  Two very small new uncontrolled trials report positive effects of rTMS on patients with TRD as assessed by decreases in HAM-D. One small study of three different intensity levels of ECT found no differences in efficacy between the two higher intensities but a lower effect on the BDI score with the lowest intensity.	<u>Tier 3:</u> A RCT (n=117) compared unilateral brief pulse (n=58) to ultra-brief pulse (n=49) ECT for clinical depression. Significantly more receiving brief pulse (68%) achieved remission (vs 49%, p = .019) according to the MADRS, and the brief pulse group achieved remission in significantly fewer sessions (M[SD] = 7.1[2.6] vs 9.2[2.3], p = .008). <sup>1</sup>

*Abbreviations:* BDI=Beck's Depression Inventory; ECT=Electroconvulsive Therapy; HAM-D=Hamilton Rating Scale for Depression; MADRS=Montgomery Asberg Depression Rating Scale; RCT=Randomized Controlled Trial; rTMS=Repetitive Transcranial Magnetic Stimulation; TRD=Treatment Resistant Depression.

Table 2. Key Question 1b: How do these nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms after two or more failed adequate trials?

Conclusions from Original Systematic Review	Findings and Assessment from prior Surveillance Assessment (August 2012)	Literature Analysis (March 2016)
---	--	----------------------------------



<a href="#">Link to Report</a>	<a href="#">Link to Report</a>	
One trial that compared the efficacy of ECT with paroxetine among a mixed MDD/bipolar population showed that ECT produced a significantly greater decrease in depressive severity (9 points by HAM-D) and significantly better response rates (71% vs. 28%) than paroxetine ( <b>SOE: Low</b> ).	<p><u>Likely Current</u></p> <p>One small trial that compared augmentation of pharmacological treatment with HFrTMS to pharmacological treatment alone found symptom reduction with the combination treatment.</p> <p>A second small trial combined TMS with positive or negative cognitive emotional reactivation or no behavioral treatment found that no reactivation or positive reactivation were associated with improvement in BDI score but negative reactivation did not lead to improvement.</p> <p>A small study of VNS implants among patients who continued pharmacotherapy found consistent positive effects on BDI and inconsistent improvement on other scales for a portion of patients.</p>	<p><u>Tier 1:</u></p> <p>A small multi-site RCT (n=73) compared ECT (n=38) to APT (n=35) for treatment resistant (no response in ≥ antidepressant or mood stabilizer trials) bipolar disorder. Results indicated that ECT was significantly more effective than APT for symptom reduction on the MADRS and the CGI-BP, and that response rates were significantly higher for participants receiving ECT. There was a non-significant trend towards shorter time to remission and response for the ECT group.<sup>2</sup></p>

*Abbreviations:* APT=Algorithm-based Pharmacological Treatment; CGI-BP=Clinical Global Impression Scale- Bipolar Disorder; ECT=Electroconvulsive Therapy; HAM-D= Hamilton Rating Scale for Depression; HFrTMS=High Frequency Repetitive Transcranial Magnetic Stimulation; MADRS= Montgomery Asberg Depression Rating Scale; MDD=Major Depressive Disorder; RCT=Randomized Controlled Trial; SOE=Strength of Evidence; TMS=Transcranial Magnetic Stimulation; VNS=Vagus Nerve Stimulation

Table 3. Key Question 2. For adults with TRD, do nonpharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence) whether as a single treatment or part of a combination treatment?

<b>Conclusions from Original Systematic Review</b> <a href="#">Link to Report</a>	<b>Findings and Assessment from prior Surveillance Assessment (August 2012)</b> <a href="#">Link to Report</a>	<b>Literature Analysis (March 2016)</b>
No head-to-head trials compared ECT, rTMS, VNS, or CBT with respect to maintaining remission (or preventing relapse).	<p><u>Likely Current</u></p> <p>One small study found rumination-focused CBT to improve remission better than treatment as usual.</p>	<p><u>Tier 3:</u></p> <p>A small phase II RCT (n=60) examined individuals with MDD who had responded to ECT and compared continuation treatment with ECT (n=25) to CBT (n=17) and antidepressants (n=18). Nearly all participants continued antidepressants during the trial. Results indicated that a significantly higher</p>

		proportion of participants receiving CBT sustained response on the HRSD-24 as compared to both ECT (77% vs. 40%, $\chi^2 = 5.43$ , $p = .02$ ) and antidepressants (77% vs. 44%, $\chi^2 = 3.74$ , $p = .05$ ). There was a non-significant trend indicating lower relapse in participants receiving CBT. Participants receiving CBT experienced significantly longer relapse-free times as compared to both ECT and antidepressants (over 12-months). <sup>3</sup>
--	--	---

*Abbreviations:* CBT=Cognitive-Behavioral Therapy; ECT=Electroconvulsive Therapy; HRSD-24= 24 Item Hamilton Rating Scale for Depression; MDD= Major Depressive Disorder; RCT=Randomized Controlled Trial; rTMS=Repetitive Transcranial Magnetic Stimulation; TRD=Treatment Resistant Depression; VNS=Vagus Nerve Stimulation

Table 4. Key Question 3: Do nonpharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic [frozen or hyper] or psychotic symptoms)?

Conclusions from Original Systematic Review <a href="#">Link to Report</a>	Findings and Assessment from prior Surveillance Assessment (August 2012) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
We identified no trials of individuals who fit our definition of treatment-resistant depression that addressed whether procedure-based treatments differed as a function of symptom subtypes. Also, no comparative evidence was available about psychotherapy in subgroups defined by symptom clusters.	<u>Likely Current</u>  One small trial of ultra-brief ECT found no difference in response between patients with unipolar depression and those with bipolar depression.	No studies were identified.

*Abbreviations:* ECT=Electroconvulsive Therapy; TRD=Treatment Resistant Depression

Table 5. Key Question 4. For adults with TRD, do nonpharmacologic interventions differ in their safety, adverse events, or adherence? Adverse effects of interest include but are not limited to amnesia, memory loss, headaches, and postoperative complications.

Conclusions from Original Systematic Review <a href="#">Link to Report</a>	Findings and Assessment from prior Surveillance Assessment (August 2012) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
In examining safety, adverse events, and adherence, we found some differences <i>across the interventions</i> in the harms and negative side effects to patients. ( <b>SOE Insufficient</b> )  <b>Cognitive functioning.</b> Some evidence suggests no differences in changes in	<u>Likely Current</u>  <b>TMS.</b> No new head-to-head studies were identified. Five small studies of TMS identified headache, scalp pain, dizziness, a combination of a foul taste and smell sensation, one report of no seizures, one case	<u>Tier 3:</u> A small phase II RCT (n=60) examined individuals who had responded to ECT and compared continuation treatment with ECT (n=25) to CBT (n=17) and antidepressants (n=18). Nearly all participants continued antidepressants during the trial. Results

<p>cognitive functioning between groups, while some evidence suggests ECT may have a deleterious impact on cognitive functioning compared to rTMS. <b>(SOE: Insufficient)</b></p> <p><b>Specific adverse events.</b> One study comparing ECT with a combination of ECT and rTMS found no differences in specific adverse events. <b>(SOE: Low)</b></p> <p><b>Withdrawals.</b> We looked at both withdrawals that investigators attributed to adverse events and overall numbers or rates of withdrawals. A single study with a small sample size indicated no difference in withdrawals due to adverse events for the ECT group when compared to rTMS but did not report on the significance of this result. <b>(SOE: Low)</b></p>	<p>of seizures in a patient with seizure history, and six cases of suicidal ideation (in patients with history of suicidal ideation). None of these studies reported on cognitive functioning. Studies that reported on withdrawals due to AEs found one withdrawal due to scalp pain, 15 due to intolerance or discomfort, five due to suicidal ideation, and one due to seizure.</p> <p><b>ECT.</b> One study reported greater impairments in verbal memory in two groups receiving higher intensity therapy than the third, lower intensity, group.</p> <p><b>VNS.</b> No serious AEs but commonly with hoarseness, dyspnea, nausea, pain, and anxiety; less frequent were cough, chest tightness, sore throat, dysphagia, and earache.</p>	<p>indicated no difference between groups on tests of cognitive function.<sup>3</sup></p> <p>A RCT (n=117) compared unilateral brief pulse (n=58) to ultra-brief pulse (n=49) ECT. There was no difference in cognitive function between groups.<sup>1</sup></p>
--	--	--

*Abbreviations:* AE=Adverse Events; CBT=Cognitive Behavioral Therapy; ECT=Electroconvulsive Therapy; HEP=Health Enhancement Program; MBCT=Mindfulness Based Cognitive Therapy; RCT=Randomized Controlled Trial; rTMS=Repetitive Transcranial Magnetic Stimulation; SOE=Strength of Evidence; TMS=Transcranial Magnetic Stimulation; VNS= Vagus Nerve Stimulation

Table 6. Key Question 5. How do the efficacy, effectiveness, or harms of treatment with nonpharmacologic treatments for TRD differ for the following subpopulations: elderly, very elderly, and other demographic groups (defined by age, ethnic or racial groups, and sex); and patients with medical comorbidities (e.g., seizure history, stroke, diabetes, dementia, perinatal depression, ischemic heart disease, cancer).

Conclusions from Original Systematic Review <a href="#">Link to Report</a>	Findings and Assessment from prior Surveillance Assessment (August 2012) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
<p>We found no studies directly comparing non-pharmacologic interventions in selected populations, such as the elderly, those with stroke, or those with other medical comorbidities.</p> <p>Two trials compared rTMS with sham, one in young adults (ages 18-37) and one in older adults with post-stroke depression. The trial in younger adults found that rTMS decreased depression severity compared with sham. The trial in older adults found that rTMS decreased</p>	<p><u>Likely Current</u></p> <p>One relatively small study of ECT among elderly with varying degrees of cognitive impairment found that those with no or mild cognitive impairment had improvement in depression symptoms at six weeks and six months, whereas those with dementia had non-significant improvement only.</p>	<p>No studies were identified.</p>

depression severity but not remission compared with the sham control.		
---	--	--

*Abbreviations:* ECT=Electroconvulsive Therapy; HAM-D= Hamilton Rating Scale for Depression; HEP=Health Enhancement Program; MBCT=Mindfulness Based Cognitive Therapy; RCT=Randomized Controlled Trial; rTMS=Repetitive Transcranial Magnetic Stimulation

Table 7. Key Question 6: For adults with TRD, do non-pharmacologic interventions differ in regard to other health-related outcomes (e.g., quality of life)?

Conclusions from Original Systematic Review <a href="#">Link to Report</a>	Findings and Assessment from prior Surveillance Assessment (August 2012) <a href="#">Link to Report</a>	Literature Analysis (March 2016)
One study found no differences between ECT and ECT+rTMS in performance on the Global Assessment of Functioning scale ( <b>SOE: Low</b> ).	<u>Likely Current</u>  One very small study of HFrTMS found increases in QOL scores for global, physical, and psychological domains but not social or environmental.	No studies were identified.

*Abbreviations:* CGI=Clinical Global Impression Scale; ECT=Electroconvulsive Therapy; HEP= Health Enhancement Program; HFrTMS=High Frequency Repetitive Transcranial Magnetic Stimulation; MBCT= Mindfulness Based Cognitive Therapy; QoL=Quality of Life; RCT=Randomized Controlled Trial; rTMS=Repetitive Transcranial Magnetic Stimulation; SOE=Strength of Evidence

### Abstracts from Relevant Literature/References

1. Spaans HP, Verwijk E, Comijs HC, et al. Efficacy and cognitive side effects after brief pulse and ultrabrief pulse right unilateral electroconvulsive therapy for major depression: a randomized, double-blind, controlled study. *The Journal of clinical psychiatry*. Nov 2013;74(11):e1029-1036.

**OBJECTIVE:** To compare the efficacy and cognitive side effects of high-dose unilateral brief pulse electroconvulsive therapy (ECT) with those of high-dose unilateral ultrabrief pulse ECT in the treatment of major depression. **METHOD:** From April 2007 until March 2011, we conducted a prospective, double-blind, randomized multicenter trial in 3 tertiary psychiatric hospitals. All patients with a depressive disorder according to DSM-IV criteria were eligible. Depression severity was assessed with the Montgomery-Asberg Depression Rating Scale; primary efficacy outcomes were response, defined as a score decrease  $\geq 60\%$  from baseline, and remission, defined as a score  $< 10$  at 2 consecutive weekly assessments. Total scores on the Autobiographical Memory Interview and Amsterdam Media Questionnaire were the primary outcome measures for retrograde amnesia. Other cognitive domains included category fluency (semantic memory) and letter fluency (lexical memory). Patients received twice-weekly unilateral brief pulse (1.0 millisecond) or ultrabrief pulse (0.3-0.4 millisecond) ECT 8 times seizure threshold until remission, for a maximum of 6 weeks. **RESULTS:** Of the 116 patients, 75% (n = 87) completed the study. Among completers, 68.4% (26/58) of those in the brief pulse group achieved remission versus 49.0% (24/49) of those in the ultrabrief pulse group (P = .019), and the brief pulse group needed fewer treatment sessions to achieve remission: mean (SD) of 7.1 (2.6)

versus 9.2 (2.3) sessions ( $P = .008$ ). No significant group differences were found in the evaluation of the cognitive assessments. CONCLUSIONS: The efficacy and speed of remission seen with high-dose brief pulse right unilateral ECT twice weekly were superior to those seen with high-dose ultrabrief pulse right unilateral ECT, with equal cognitive side effects as defined by retrograde amnesia, semantic memory, and lexical memory. TRIAL REGISTRATION: Netherlands National Trial Register number: NTR1304.

---

2. Schoeyen HK, Kessler U, Andreassen OA, et al. Treatment-resistant bipolar depression: a randomized controlled trial of electroconvulsive therapy versus algorithm-based pharmacological treatment. *The American journal of psychiatry*. Jan 2015;172(1):41-51.

OBJECTIVE: Electroconvulsive therapy (ECT) is regarded by many clinicians as the most effective treatment for treatment-resistant bipolar depression, but no randomized controlled trials have been conducted, to the authors' knowledge. They compared efficacy measures of ECT and algorithm-based pharmacological treatment in treatment-resistant bipolar depression. METHOD: This multicenter, randomized controlled trial was carried out at seven acute-care psychiatric inpatient clinics throughout Norway and included 73 bipolar disorder patients with treatment-resistant depression. The patients were randomly assigned to receive either ECT or algorithm-based pharmacological treatment. ECT included three sessions per week for up to 6 weeks, right unilateral placement of stimulus electrodes, and brief pulse stimulation. RESULTS: Linear mixed-effects modeling analysis revealed that ECT was significantly more effective than algorithm-based pharmacological treatment. The mean scores at the end of the 6-week treatment period were lower for the ECT group than for the pharmacological treatment group: by 6.6 points on the Montgomery-Asberg Depression Rating Scale ( $SE=2.05$ , 95%  $CI=2.5-10.6$ ), by 9.4 points on the 30-item version of the Inventory of Depressive Symptomatology-Clinician-Rated ( $SE=2.49$ , 95%  $CI=4.6-14.3$ ), and by 0.7 points on the Clinical Global Impression for Bipolar Disorder ( $SE=0.31$ , 95%  $CI=0.13-1.36$ ). The response rate was significantly higher in the ECT group than in the group that received algorithm-based pharmacological treatment (73.9% versus 35.0%), but the remission rate did not differ between the groups (34.8% versus 30.0%). CONCLUSION: Remission rates remained modest regardless of treatment choice for this challenging clinical condition.

---

3. Brakemeier EL, Merkl A, Wilbertz G, et al. Cognitive-behavioral therapy as continuation treatment to sustain response after electroconvulsive therapy in depression: a randomized controlled trial. *Biological psychiatry*. Aug 1 2014;76(3):194-202.

BACKGROUND: Although electroconvulsive therapy (ECT) is the most effective acute antidepressant intervention, sustained response rates are low. It has never been systematically assessed whether psychotherapy, continuation ECT, or antidepressant medication is the most efficacious intervention to maintain initial treatment response. METHODS: In a prospective, randomized clinical trial, 90 inpatients with major depressive disorder (MDD) were treated with right unilateral ultra-brief acute ECT. Electroconvulsive therapy responders received 6 months guideline-based antidepressant medication (MED) and were randomly

assigned to add-on therapy with cognitive-behavioral group therapy (CBT-arm), add-on therapy with ultra-brief pulse continuation electroconvulsive therapy (ECT-arm), or no add-on therapy (MED-arm). After the 6 months of continuation treatment, patients were followed-up for another 6 months. The primary outcome parameter was the proportion of patients who remained well after 12 months. RESULTS: Of 90 MDD patients starting the acute phase, 70% responded and 47% remitted to acute ECT. After 6 months of continuation treatment, significant differences were observed in the three treatment arms with sustained response rates of 77% in the CBT-arm, 40% in the ECT-arm, and 44% in the MED-arm. After 12 months, these differences remained stable with sustained response rates of 65% in the CBT-arm, 28% in the ECT-arm, and 33% in the MED-arm. CONCLUSIONS: These results suggest that ultra-brief pulse ECT as a continuation treatment correlates with low sustained response rates. However, the main finding implicates cognitive-behavioral group therapy in combination with antidepressants might be an effective continuation treatment to sustain response after successful ECT in MDD patients.

## Appendix E. Summary Tables\*

Table 1. Key Question 1a: For adults with treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic [i.e., pharmacologic] intervention), do non-pharmacologic interventions such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), or demonstrated effective psychotherapy (e.g., cognitive therapy [CBT or IPT]) differ in efficacy or effectiveness in treating acute phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?

Conclusions from the Original Systematic Review** <a href="#">Link to Report</a>	Findings and Conclusions from Prior Surveillance Assessment (August 2012) <a href="#">Link to Report</a>	Current Literature Search (March 2016)	Expert Opinion	Surveillance Assessment
A very small number of head-to-head trials have shown no differences between ECT and rTMS or ECT and ECT+rTMS for depressive severity, response rates, and remission rates. No trial involved a direct comparison of psychotherapy with another non-pharmacologic intervention.	<u>Likely Current</u>  Two very small new uncontrolled trials report positive effects of rTMS on patients with TRD as assessed by decreases in HAM-D. One small study of three different intensity levels of ECT found no differences in efficacy between the two higher intensities but a lower effect on the BDI score with the lowest intensity.	<u>Tier 3:</u> A RCT (n=117) compared unilateral brief pulse (n=58) to ultra-brief pulse (n=49) ECT for clinical depression. Significantly more receiving brief pulse (68%) achieved remission (vs 49%, $p = .019$ ) according to the MADRS, and the brief pulse group achieved remission in significantly fewer sessions ( $M[SD] = 7.1[2.6]$ vs $9.2[2.3]$ , $p = .008$ ). <sup>1</sup>	One reviewer did not comment on the currency of the original review conclusions, but suggested a (Tier 1) study: A RCT (n=131 completed) compared MBCT to HEP as an adjunct to antidepressants for treatment resistant depression (2+ trials for current episode). At eight weeks, MBCT was associated with greater reduction in depression severity (36.6 vs. 25.3%; $p=0.01$ ) and significantly more responders (30.3 vs. 15.3%; $p=0.03$ ) on the HAM-D. There was no significant difference in rates of remission. At 52 weeks, MBCT was associated with a larger percentage of treatment responses, but not a reduction in severity or	This portion of the systematic review may not be current due to one study identified by an expert which found MBCT to be associated better outcomes than HEP. No Tier 1 studies comparing psychotherapy were identified in the original review.

			<p>rates of remission.<sup>2</sup></p> <p>A second reviewer believed the original review to be current, and suggested two studies. One was excluded, as it did not meet inclusion criteria for intervention.<sup>3</sup></p> <p>The second was also excluded because participants did not meet inclusion criteria for treatment resistant depression (Tiers 1-3).<sup>4</sup></p>	
--	--	--	---	--

\*No relevant FDA warnings were identified. \*\* SOE relates to Tier 1 studies only *Abbreviations:* BDI=Beck's Depression Inventory; CBT=Cognitive Behavioral Therapy; ECT=Electroconvulsive Therapy; HAM-D=Hamilton Rating Scale for Depression; HEP= Health Enhancement Program; IPT=Interpersonal Therapy; MADRS= Montgomery Asberg Depression Rating Scale; MBCT=Mindfulness Based Cognitive Therapy; RCT=Randomized Controlled Trial; rTMS=Repetitive Transcranial Magnetic Stimulation; TRD=Treatment Resistant Depression.

Table 2. Key Question 1b: How do these nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms after two or more failed adequate trials?

<b>Conclusions from the Original Systematic Review**</b> <a href="#">Link to Report</a>	<b>Findings and Conclusions from Prior Surveillance Assessment (August 2012)</b> <a href="#">Link to Report</a>	<b>Current Literature Search (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
One trial that compared the efficacy of ECT with paroxetine among a mixed MDD/bipolar population showed that ECT produced a significantly greater decrease in depressive severity (nine points by HAM-D) and significantly better response rates (71% vs. 28%) than paroxetine	<p><u>Likely Current</u></p> <p>One small trial that compared augmentation of pharmacological treatment with HFrTMS to pharmacological treatment alone found symptom reduction with the combination treatment.</p> <p>A second small trial found</p>	<p><u>Tier 1:</u></p> <p>A small multi-site RCT (n=73) compared ECT (n=38) to APT (n=35) for treatment resistant (no response in <math>\geq 2</math> antidepressant or mood stabilizer trials) bipolar disorder. Results indicated that ECT was significantly more effective than APT for symptom reduction on</p>	One reviewer did not comment on the currency of the original review conclusions, and the second reviewer stated “no data.”	This portion of the original systematic review is likely current.



(SOE: Low).	<p>similar results with aTMS<sup>7</sup> A trial that combined TMS with positive or negative cognitive-emotional reactivation or no behavioral treatment found that no reactivation or positive reactivation were associated with improvement in BDI score but negative reactivation did not lead to improvement.</p> <p>A small study of VNS implants among patients who continued pharmacotherapy found consistent positive effects on BDI and inconsistent improvement on other scales for a portion of patients.</p>	the MADRS and the CGI-BP, and that response rates were significantly higher for participants receiving ECT. There was a non-significant trend towards shorter time to remission and response for the ECT group. <sup>5</sup>		
-------------	--	--	--	--

\*No relevant FDA warnings were identified. \*\* SOE relates to Tier 1 studies only *Abbreviations:* APT=Algorithm-based Pharmacological Treatment; CGI-BP=Clinical Global Impression Scale- Bipolar Disorder; ECT=Electroconvulsive Therapy; HAM-D= Hamilton Rating Scale for Depression; HFrTMS=High Frequency Repetitive Transcranial Magnetic Stimulation; MADRS= Montgomery Asberg Depression Rating Scale; MDD=Major Depressive Disorder; RCT=Randomized Controlled Trial; SOE=Strength of Evidence; TMS=Transcranial Magnetic Stimulation; VNS=Vagus Nerve Stimulation

Table 3. Key Question 2. For adults with TRD, do nonpharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence) whether as a single treatment or part of a combination treatment?

Conclusions from the Original Systematic Review** <a href="#">Link to Report</a>	Findings and Conclusions from Prior Surveillance Assessment (August 2012) <a href="#">Link to Report</a>	Current Literature Search (March 2016)	Expert Opinion	Surveillance Assessment
No head-to-head trials compared ECT, rTMS, VNS, or CBT with respect to maintaining remission	<u>Likely Current</u>  One small study found rumination-focused CBT to	Tier 3: A small phase II RCT (n=60) examined individuals with MDD who	One reviewer did not comment on the currency of the original review conclusions. A second	This portion of the original systematic review is likely current. However, we identified a Tier 3 study

(or preventing relapse).	improve remission better than treatment as usual.	had responded to ECT and compared continuation treatment with ECT (n=25) to CBT (n=17) and antidepressants (n=18). Nearly all participants continued antidepressants during the trial. Results indicated that a significantly higher proportion of participants receiving CBT sustained response on the HRSD-24 as compared to both ECT (77% vs. 40%, $\chi^2 = 5.43$ , $p = .02$ ) and antidepressants (77% vs. 44%, $\chi^2 = 3.74$ , $p = .05$ ). There was a non-significant trend indicating lower relapse in participants receiving CBT. Participants receiving CBT experienced significantly longer relapse-free times as compared to both ECT and antidepressants (over 12-months). <sup>6</sup>	reviewer believed the original review to be current, and suggested two studies. One was excluded, as it did not meet inclusion criteria for intervention. <sup>3</sup> The second was also excluded because participants did not meet inclusion criteria for treatment resistant depression (Tiers 1-3). <sup>4</sup>	comparing ECT to CBT and antidepressants, which found that CBT was more effective than ECT or antidepressants alone for sustained response and longer relapse free times.
--------------------------	---	--	---	---

\*No relevant FDA warnings were identified. \*\* SOE relates to Tier 1 studies only *Abbreviations:* CBT=Cognitive-Behavioral Therapy; ECT=Electroconvulsive Therapy; HRSD-24= 24 Item Hamilton Depression Rating Scale; MDD= Major Depressive Disorder; RCT=Randomized Controlled Trial; rTMS=Repetitive Transcranial Magnetic Stimulation; TRD=Treatment Resistant Depression; VNS=Vagus Nerve Stimulation

Table 4. Key Question 3: Do nonpharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic [frozen or hyper] or psychotic symptoms?)

Conclusions from the Original Systematic Review** <a href="#">Link to Report</a>	Findings and Conclusions from Prior Surveillance Assessment (August 2012) <a href="#">Link to Report</a>	Current Literature Search (March 2016)	Expert Opinion	Surveillance Assessment
We identified no trials of individuals who fit our	<a href="#">Likely Current</a>	No studies were identified.	One reviewer did not comment on the currency	This portion of the original systematic review is likely

definition of treatment-resistant depression that addressed whether procedure-based treatments differed as a function of symptom subtypes. Also, no comparative evidence was available about psychotherapy in subgroups defined by symptom clusters.	One small trial of ultra-brief ECT found no difference in response between patients with unipolar depression and those with bipolar depression.		of the original review conclusions, and the second reviewer stated “no data.”	current.
--	---	--	---	----------

\*No relevant FDA warnings were identified. \*\* SOE relates to Tier 1 studies only *Abbreviations:* ECT=Electroconvulsive Therapy; TRD=Treatment Resistant Depression

Table 5. Key Question 4. For adults with TRD, do nonpharmacologic interventions differ in their safety, adverse events, or adherence? Adverse effects of interest include but are not limited to amnesia, memory loss, headaches, and postoperative complications.

<b>Conclusions from the Original Systematic Review**</b> <a href="#">Link to Report</a>	<b>Findings and Conclusions from Prior Surveillance Assessment (August 2012)</b> <a href="#">Link to Report</a>	<b>Current Literature Search (March 2016)</b>	<b>Expert Opinion</b>	<b>Surveillance Assessment</b>
In examining safety, adverse events, and adherence, we found some differences <i>across the interventions</i> in the harms and negative side effects to patients. ( <b>SOE Insufficient</b> )  <b>Cognitive functioning.</b> Some evidence suggests no differences in changes in cognitive functioning between groups, while some evidence suggests ECT may have a deleterious impact on cognitive functioning	<u>Likely Current</u>  <b>TMS.</b> No new head-to-head studies were identified. Five small studies of TMS identified headache, scalp pain, dizziness, a combination of a foul taste and smell sensation, one report of no seizures, one case of seizures in a pt. with seizure History, and six cases of suicidal ideation (in patients with history of suicidal ideation). None of these studies reported on cognitive functioning.	<u>Tier 3:</u> A small phase II RCT (n=60) examined individuals who had responded to ECT and compared continuation treatment with ECT (n=25) to CBT (n=17) and antidepressants (n=18). Nearly all participants continued antidepressants during the trial. Results indicated no difference between groups on tests of cognitive function. <sup>6</sup>  A RCT (n=117) compared unilateral brief pulse	One reviewer did not comment on the currency of the original review conclusions, but suggested a (Tier 1) study: A RCT (n=131 completed) compared MBCT to HEP as an adjunct to antidepressants for treatment resistant depression (2+ trials for current episode). There was no significant difference in adherence between groups. <sup>2</sup>  The second reviewer stated “no data.”	This portion of the original systematic review is likely current. However, consistent with the findings of studies in the original review two studies we identified found no difference in cognitive functioning associated with ECT. We also identified one study that found no difference in adherence when comparing MBCT to HEP.

<p>compared to rTMS. (SOE: Insufficient)</p> <p><b>Specific adverse events.</b> One study comparing ECT with a combination of ECT and rTMS found no differences in specific adverse events. (SOE: Low)</p> <p><b>Withdrawals.</b> We looked at both withdrawals that investigators attributed to adverse events and overall numbers or rates of withdrawals. A single study with a small sample size indicated no difference in withdrawals due to adverse events for the ECT group when compared to rTMS but did not report on the significance of this result. (SOE: Low)</p>	<p>Studies that reported on withdrawals due to AEs found one withdrawal due to scalp pain, 15 due to intolerance or discomfort, five due to suicidal ideation, and one due to seizure.</p> <p><b>ECT.</b> One study reported greater impairments in verbal memory in two groups receiving higher intensity therapy than the third, lower intensity, group.</p> <p><b>VNS.</b> No serious AEs but commonly with hoarseness, dyspnea, nausea, pain, and anxiety; less frequent were cough, chest tightness, sore throat, dysphagia, and earache.</p>	<p>(n=58) to ultra-brief pulse (n=49) ECT. There was no difference in cognitive function between groups.<sup>1</sup></p>		
---	--	--	--	--

\*No relevant FDA warnings were identified. \*\* SOE relates to Tier 1 studies only *Abbreviations:* AE=Adverse Events; CBT=Cognitive Behavioral Therapy; ECT=Electroconvulsive Therapy; HEP=Health Enhancement Program; MBCT=Mindfulness Based Cognitive Therapy; RCT=Randomized Controlled Trial; rTMS=Repetitive Transcranial Magnetic Stimulation; SOE=Strength of Evidence; TMS=Transcranial Magnetic Stimulation

Table 6. Key Question 5. How do the efficacy, effectiveness, or harms of treatment with nonpharmacologic treatments for TRD differ for the following subpopulations: elderly, very elderly, and other demographic groups (defined by age, ethnic or racial groups, and sex); and patients with medical comorbidities (e.g., seizure history, stroke, diabetes, dementia, perinatal depression, ischemic heart disease, cancer).

Conclusions from the Original Systematic Review** <a href="#">Link to Report</a>	Findings and Conclusions from Prior Surveillance Assessment (August 2012) <a href="#">Link to Report</a>	Current Literature Search (March 2016)	Expert Opinion	Surveillance Assessment
We found no studies	Likely Current	No studies were identified.	One reviewer did not	This portion of the

<p>directly comparing non-pharmacologic interventions in selected populations, such as the elderly, those with stroke, or those with other medical comorbidities.</p> <p>Two trials compared rTMS with sham, one in young adults (ages 18– 37) and one in older adults with post-stroke depression. The trial in younger adults found that rTMS decreased depression severity compared with sham. The trial in older adults found that rTMS decreased depression severity but not remission compared with the sham control.</p>	<p>One relatively small study of ECT among elderly with varying degrees of cognitive impairment found that those with no or mild cognitive impairment had improvement in depression symptoms at six weeks and six months, whereas those with dementia had non-significant improvement only.</p>		<p>comment on the currency of the original review conclusions, but suggested a (Tier 1) study: A RCT (n=131 completed) compared MBCT to HEP as an adjunct to antidepressants for treatment resistant depression (2+ trails for current episode). At eight weeks, MBCT was associated with greater reduction in depression severity (36.6 vs. 25.3%; p=0.01) and significantly more responders (30.3 vs. 15.3%; p=0.03) on the HAM-D. There was no significant difference in rates of remission. At 52 weeks, MBCT was associated with a larger percentage of treatment responses, but not a reduction in severity or rates of remission. A comorbid personality disorder or anxiety was associated with a reduction in HAM-D response, but there was no significant interaction with condition. There was no difference by gender, sociodemographic group, education, or medical comorbidity.<sup>2</sup></p> <p>The second expert stated “no data.”</p>	<p>systematic review may not be current due to one study identified by an expert which found that personality disorder and anxiety were related to poorer outcomes, with no difference associated with other demographic and medical variables. No Tier 1 studies comparing psychotherapy were identified in the original review.</p>
---	---	--	--	---

\*No relevant FDA warnings were identified. \*\* SOE relates to Tier 1 studies only *Abbreviations:* ECT=Electroconvulsive Therapy; HAM-D=Hamilton Rating Scale for Depression; HEP=Health Enhancement Program; MBCT=Mindfulness Based Cognitive Therapy; RCT=Randomized Controlled Trial; rTMS=Repetitive Transcranial Magnetic Stimulation

Table 7. Key Question 6: For adults with TRD, do non-pharmacologic interventions differ in regard to other health-related outcomes (e.g., quality of life)?

Conclusions from the Original Systematic Review** <a href="#">Link to Report</a>	Findings and Conclusions from Prior Surveillance Assessment (August 2012) <a href="#">Link to Report</a>	Current Literature Search (March 2016)	Expert Opinion	Surveillance Assessment
One study found no differences between ECT and ECT+rTMS in performance on the Global Assessment of Functioning scale ( <b>SOE: Low</b> ).	<u>Likely Current</u>  One very small study of HFrTMS found increases in QoL scores for global, physical, and psychological domains but not social or environmental.	No studies were identified.	One reviewer did not comment on the currency of the original review conclusions, but suggested a (Tier 1) study: A RCT (n=131 completed) compared MBCT to HEP as an adjunct to antidepressants for treatment resistant depression (2+ trials for current episode). At eight weeks, both groups achieved better scores on the CGI; however, participants receiving MBCT experienced significantly greater improvement (p=.001), and decreased severity (p=.038). At 52 weeks, both groups improved significantly from baseline, but there was no difference between groups. <sup>2</sup>  A second reviewer believed the original review	This portion of the systematic review may not be current due to one study identified by an expert which found MBCT to be associated better outcomes than HEP at 8 weeks. Both MBCT and HEP were associated with improvement on the CGI at eight and 52 weeks. No Tier 1 studies comparing psychotherapy were identified in the original review.

			to be current, and suggested two studies. One was excluded, as did not meet inclusion criteria for intervention. <sup>3</sup> The second was also excluded because participants did not meet inclusion criteria for treatment resistant depression (Tiers 1-3). <sup>4</sup>	
--	--	--	--	--

\*No relevant FDA warnings were identified. \*\* SOE relates to Tier 1 studies only. *Abbreviations:* CGI=Clinical Global Impression Scale; ECT=Electroconvulsive Therapy; HEP= Health Enhancement Program; HFrTMS=High Frequency Repetitive Transcranial Magnetic Stimulation; MBCT= Mindfulness Based Cognitive Therapy; QoL=Quality of Life; RCT=Randomized Controlled Trial; rTMS=Repetitive Transcranial Magnetic Stimulation; SOE=Strength of Evidence

## References

1. \$Spaans HP, Verwijk E, Comijs HC, et al. Efficacy and cognitive side effects after brief pulse and ultrabrief pulse right unilateral electroconvulsive therapy for major depression: a randomized, double-blind, controlled study. *The Journal of clinical psychiatry*. Nov 2013;74(11):e1029-1036.
2. \$Eisendrath SJ, Gillung E, Delucchi KL, et al. A Randomized Controlled Trial of Mindfulness-Based Cognitive Therapy for Treatment-Resistant Depression. *Psychotherapy and psychosomatics*. 2016;85(2):99-110.
3. \$Fonagy P, Rost F, Carlyle JA, et al. Pragmatic randomized controlled trial of long-term psychoanalytic psychotherapy for treatment-resistant depression: the Tavistock Adult Depression Study (TADS). *World Psychiatry*. 2015;14:10.
4. \$Wiles NJ, Thomas L, Turner N, et al. Long-term effectiveness and cost-effectiveness of cognitive behavioural therapy as an adjunct to pharmacotherapy for treatment-resistant depression in primary care: follow-up of the CoBaIT randomised controlled trial. *The Lancet Psychiatry*. 2016;3(2):137-144.
5. \$Schoeyen HK, Kessler U, Andreassen OA, et al. Treatment-resistant bipolar depression: a randomized controlled trial of electroconvulsive therapy versus algorithm-based pharmacological treatment. *The American journal of psychiatry*. Jan 2015;172(1):41-51.
6. \$Brakemeier EL, Merkl A, Wilbertz G, et al. Cognitive-behavioral therapy as continuation treatment to sustain response after electroconvulsive therapy in depression: a randomized controlled trial. *Biological psychiatry*. Aug 1 2014;76(3):194-202.

