Appendix C. Literature Search Results

- 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.
- 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.
- 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.
- 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 CoBalT Trial. *The British journal of psychiatry: the journal of mental science.* Jan 2014;204(1):69-76.

  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.

  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.

  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.

  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).[9]

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,[9] or between unilateral brief pulse and ultra-brief pulse ECT.[5]

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 **Link to Report**	**Findings and Assessment from prior Surveillance Assessment (August 2012)** **Link to Report**	**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.	Likely Current 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.	Tier 3: 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).[1]

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)**

Link to Report	Link to Report	
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 (**SOE: Low**).	Likely Current One small trial that compared augmentation of pharmacological treatment with HFrTMS to pharmacological treatment alone found symptom reduction with the combination treatment. 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. 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.	Tier 1: 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.[2]

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 Original Systematic Review **Link to Report**	**Findings and Assessment from prior Surveillance Assessment (August 2012)** **Link to Report**	**Literature Analysis (March 2016)**
No head-to-head trials compared ECT, rTMS, VNS, or CBT with respect to maintaining remission (or preventing relapse).	Likely Current One small study found rumination-focused CBT to improve remission better than treatment as usual.	Tier 3: 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

		proportion of participants receiving CBT sustained response on the HRSD-24 as compared to both ECT (77% vs. 40%, x^2 = 5.43, p = .02) and antidepressants (77% vs. 44%, x^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).[3]

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 **Link to Report**	**Findings and Assessment from prior Surveillance Assessment (August 2012)** **Link to Report**	**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.	Likely Current 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 **Link to Report**	**Findings and Assessment from prior Surveillance Assessment (August 2012)** **Link to Report**	**Literature Analysis (March 2016)**
In examining safety, adverse events, and adherence, we found some differences *across the interventions* in the harms and negative side effects to patients. (**SOE Insufficient**) **Cognitive functioning.** Some evidence suggests no differences in changes in	Likely Current **TMS.** 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	Tier 3: 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

cognitive functioning between groups, while some evidence suggests ECT may have a deleterious impact on cognitive functioning compared to rTMS. (**SOE: Insufficient**) **Specific adverse events.** One study comparing ECT with a combination of ECT and rTMS found no differences in specific adverse events. (**SOE: Low**) **Withdrawals.** 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**)	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. **ECT.** One study reported greater impairments in verbal memory in two groups receiving higher intensity therapy than the third, lower intensity, group. **VNS.** No serious AEs but commonly with hoarseness, dyspnea, nausea, pain, and anxiety; less frequent were cough, chest tightness, sore throat, dysphagia, and earache.	indicated no difference between groups on tests of cognitive function.[3] 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.[1]

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 **Link to Report**	**Findings and Assessment from prior Surveillance Assessment (August 2012)** **Link to Report**	**Literature Analysis (March 2016)**
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. 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	Likely Current 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.	No studies were identified.

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 **Link to Report**	**Findings and Assessment from prior Surveillance Assessment (August 2012)** **Link to Report**	**Literature Analysis (March 2016)**
One study found no differences between ECT and ECT+rTMS in performance on the Global Assessment of Functioning scale (**SOE: Low**).	Likely Current 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 >/= 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.

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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.

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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** **Link to Report**	**Findings and Conclusions from Prior Surveillance Assessment (August 2012)** **Link to Report**	**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.	Likely Current 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.	Tier 3: 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).[1]	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+ 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	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.

			rates of remission.[2] 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.[3] The second was also excluded because participants did not meet inclusion criteria for treatment resistant depression (Tiers 1-3).[4]	

*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?

Conclusions from the Original Systematic Review Link to Report**	**Findings and Conclusions from Prior Surveillance Assessment (August 2012)** Link to Report	**Current Literature Search (March 2016)**	**Expert Opinion**	**Surveillance Assessment**
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	Likely Current One small trial that compared augmentation of pharmacological treatment with HFrTMS to pharmacological treatment alone found symptom reduction with the combination treatment. A second small trial found	Tier 1: A small multi-site RCT (n=73) compared ECT (n=38) to APT (n=35) for treatment resistant (no response in ≥ 2 antidepressant or mood stabilizer trials) bipolar disorder. Results indicated that ECT was significantly more effective than APT for symptom reduction on	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.