Nonpharmacologic Treatments for Treatment-Resistant Depression

Draft Key Questions: Public Comments and Response

November 8, 2013
Nonpharmacologic Treatments for Treatment-Resistant Depression

Response to Topic and Public Comments on Key Questions

November 8, 2013

Prepared by:

Hayes, Inc.
157 S. Broad Street Suite 200
Lansdale, PA 19446
Response to Public Comments, Topic and Key Questions

Nonpharmacological Treatments for Treatment-Resistant Depression

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

Draft key questions for each WA HTA report are posted online in order to gather public input and any additional evidence to be considered in the evidence review. Since key questions guide the evidence report, WA HTA seeks input on whether the questions are appropriate to address its mandate to gather evidence on safety, efficacy, and cost-effectiveness relevant to coverage determinations. Input about the following is especially helpful:

- Are appropriate populations or indications identified?
- Are appropriate comparators identified?
- Are appropriate patient-oriented outcome measures included?
- Are there special policy or clinical considerations that could affect the review?

Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only. When comments cited evidence, the vendor was encouraged to consider inclusion of this evidence in the report.

This document responds to comments from the following parties:

- David H. Avery, M.D.; Professor Emeritus, University of Washington School of Medicine, Psychiatric Medicine Associates
- Charissa Fotinos, M.D., M.Sc.; Assistant Chief Medical Officer, Washington Health Care Authority

Table 1 provides a summary of comments with responses.
Table 1. Public Comments on Topic and Key Questions, Nonpharmacologic Treatments for Treatment-Resistant Depression

<table>
<thead>
<tr>
<th>Comment and Source</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comments on Topic</strong></td>
<td></td>
</tr>
<tr>
<td>None received.</td>
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</tr>
<tr>
<td><strong>Comments on Draft Key Questions</strong></td>
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</tbody>
</table>

**October 3, 2013 Letter from David Avery, M.D.**

"Personal Perspective: I retired from the University of Washington as Professor Emeritus in 2012 and am now in private practice. I administer ECT to about 2 patients per month. As a young doctor, I did research on ECT that found that ECT was more effective than antidepressant medication and that ECT lowers the mortality rate in depression compared to patients with depression not treated with ECT. I was Director of the Inpatient Psychiatry Service for most of the years from 1980 to 2012 and Director of the ECT Service at Harborview Medical Center from 1980 to 2012. It was very gratifying to see patients respond well to ECT. However, it was also a challenge to provide this service to the Medicaid population in Western Washington. Over the last 7 years, Harborview has been the only hospital in Western Washington to offer ECT to Medicaid patients. I had heard from other clinicians that the primary reason that other hospitals stopped this service was because of the poor reimbursement for ECT from Medicaid. Harborview Medical Center was probably offering ECT to Medicare patients at a financial loss. Now, with limited bed availability at Harborview, many patients who would benefit from ECT do not have ECT available to them. It is unfortunate that Medicaid patients do not have access to the most effective treatment for major depression."

**Key Question 1a**

"There is not one standard definition of treatment-resistance and is often used interchangeably with the term “medication-resistance”. Medication-resistance often refers to patients with depression who have failed to respond to at least two adequate courses of antidepressant medication. In the STAR*D study in which sequential antidepressant medications were administered, the probability of responding to an antidepressant trial decreased with the number of previous failed trials. For example, the remission rate after an adequate antidepressant of citalopram and a group of depressed patients who had never been treated with a depressant medication was 37%. Among those who failed to respond to citalopram, the next antidepressant trial resulted in a 31% remission rate. Among those who failed the second trial, the next antidepressant trial resulted in only a 14% remission. In those who failed three antidepressant trials, the remission rate was 13%."

Thank you for your comments. The STAR*D study will be summarized in the report. This key question is removed. Information addressing diagnostic/condition definitions will be summarized in the background section of the report."
<table>
<thead>
<tr>
<th>Key Question 1b</th>
<th>Comment and Source</th>
<th>Response</th>
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<tbody>
<tr>
<td>&quot;In the literature concerning major depressive disorder, response and remission are the two major categories that have been used to measure improvement. “Response” has typically been defined as at least a 50% reduction in the depression rating scale. The most commonly used depression ratings are the Hamilton Depression Rating Scale and the Montgomery-Asberg Depression Rating Scale (MADRS). “Remission” is typically defined as a Hamilton Depression Rating of less than eight or a MADRS of less than 10.”</td>
<td>Thank you for your comments. This key question is removed. Information addressing specific instruments and clinically meaningful change will be summarized in the background section of the report.</td>
<td></td>
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<table>
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<tr>
<th>Key Question 2a</th>
<th>Comment and Source</th>
<th>Response</th>
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</thead>
<tbody>
<tr>
<td>The commenter summarized findings from several reviews and clinical trials with respect to the interventions of interest.</td>
<td>Thank you for these comments and citations. The references will be considered for inclusion in the report.</td>
<td></td>
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<table>
<thead>
<tr>
<th>Key Question 2b</th>
<th>Comment and Source</th>
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<tbody>
<tr>
<td>“ECT- The major development in ECT over the past 10 years has been the introduction of ultra-brief right unilateral ECT. This technique has been shown to be as effective as by temporal ECT with much less memory disturbance.&quot; The right unilateral technique is intensity dependent. Patients treated with right unilateral ECT at a stimulus intensity of six times the seizure threshold are more likely to remit than those treated at seizure threshold. Some studies have shown this treatment to be as effective as bitemporal ECT. The average duration of treatment is about three weeks. Typically three ECT sessions are given per week. The average number of sessions is eight or nine. ECT is very effective even when not given with an antidepressant medication. However, the addition of an antidepressant medication may augment the ECT response. rTMS- The effectiveness of rTMS increases with the number of rTMS sessions. It may be necessary to have as many as 30 TMS sessions. Initial studies of TMS were probably underdosed. Many of those studies looked at the effectiveness of only 10 or 15 TMS sessions. More recent data indicate that by increasing the number of sessions or the number of pulses per session can significantly increase the effectiveness of TMS. Initial studies of TMS required that patients discontinue their current antidepressant medication. In practice TMS is now primarily used as an augmentation strategy for antidepressant medication that has either been not effective or only partially effective. The response and remission rates in these studies are</td>
<td>Thank you for this helpful background information. No change to Key Question.</td>
<td></td>
</tr>
</tbody>
</table>
clearly greater than in the studies of rTMS that required discontinuation of the antidepressant medication. See the powerpoint presentation for further references.

DBS- I’ve not researched the literature on these issues in the brain stimulation.

tDCS- I’ve not researched the literature on these issues in direct current stimulation.”

**Key Question 3**

“ECT- The potential side effects of electroconvulsive therapy have been well studied. The side effects of been summarized well in Up-To-Date. Patients may experience a temporary memory disturbance. As noted above, this memory disturbance has been markedly decreased with the introduction of the ultra-brief right unilateral technique. While memory disturbance can occur with ECT, the cognitive problems associated with depression, should not be underestimated. Because ECT is very effective in treating depression, on average patients experience an improvement in neurocognitive functioning. Patients receiving ECT may experience a headache, nausea, muscle soreness, and temporary disorientation following an ECT session. The mortality rate from ECT is very low, approximately one in 10,000 or one and 20,000 treatments. Because depression is associated with increased mortality, ECT is associated with a reduction in mortality rates in depressed populations compared to depressed patients who did not receive ECT.15

rTMS- rTMS has a very good side effect profile that is described in the powerpoint.

DBS- The side effects are described well in Up-To-Date.

tDCS- I am not familiar with the side effects of tDCS.”

**Key Question 4**

“ECT- ECT has been found effective across a wide range of subpopulations16. ECT may be more effective in older depressed patients and in depressed patients with psychotic features compared to non-psychotic depressed patients. ECT is equally effective in unipolar and bipolar depressed patients. As noted above, some studies show that medication resistance significantly worsens the response to ECT; others do not.

Thank you for this background. The reference will be considered for inclusion in the report.

No change in the Key Question.
<table>
<thead>
<tr>
<th>Comment and Source</th>
<th>Response</th>
</tr>
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<tbody>
<tr>
<td>rTMS- rTMS appears be effective primarily in non-psychotic depressed patients. DBS- I am not familiar with the efficacy of DBS in subpopulations. tDCS- I am not familiar with the efficacy of tDCS in subpopulations.”</td>
<td></td>
</tr>
</tbody>
</table>

**Key Question 5**

“ECT- Although ECT is more expensive than an antidepressant medication, ECT is cost-effective for selected patients. Because ECT is more effective and works more quickly than antidepressant medication, ECT can decrease the duration of hospitalization and markedly lower those costs. For depressed outpatients, ECT’s effectiveness can decrease the number of antidepressant trials and the associated outpatient visits and medication costs. In addition, maintenance ECT is able to lower the risk of rehospitalization rates and lower costs.17 Cost-effectiveness should take into account the degree of medication-resistance of the patient population.18 Increasing medication resistance increases the health care costs. Although the initial costs of ECT are greater than for rTMS, ECT was found more cost-effective than rTMS in one British study.19

rTMS- Although the initial costs of ECT are greater than for rTMS, ECT was found more cost-effective than rTMS in one British study.19

DBS- I am not familiar with cost-effectiveness studies of DBS.

tDCS- I am not familiar with cost-effectiveness studies of tDCS.”

The commenter also supplied a set of PowerPoint slides with information about ECT and data from various studies.

Thank you for this additional resource.

**Comments from Charissa Fotinos, M.D.**

“How is adequate being defined?” [A question regarding a statement in the Introduction to the Draft Key Questions about “emerging consensus that failure of ≥ 2 prior adequate pharmacologic trials is an appropriate definition.”]

No a priori definition is assumed. The report will describe how the included studies defined “adequate trials.”

No change to Key Questions.
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Key Question 1b</strong>&lt;br&gt;“Would the definition for meaningful improvement in depression or function be different in treatment resistant depression than in regular depression? My guess is there is likely not a separate tool.”</td>
<td>Thank you for this insight. The report will clarify whether measurement tools are specific to TRD. Key question removed: information will be summarized in background section of report.</td>
</tr>
<tr>
<td><strong>Key Question 3</strong>&lt;br&gt;“I might make this a 2 part question. What adverse events are associated with nonRx treatments and what are the withdrawal rates due to 1)adverse events and 2)lack of benefit? I don't see the later reason as an adverse event per se.”</td>
<td>Thank you for this thoughtful response.</td>
</tr>
</tbody>
</table>
October 3, 2013

Dear Ms. Masters,

Thank you for the opportunity to comment on nonpharmacologic treatments for treatment-resistant depression. Below are my responses to the Key Questions. I have also included a powerpoint presentation on this topic as an attachment. This powerpoint is a compilation of slides from lectures that I give to University of Washington psychiatry residents. This presentation goes into a little more detail concerning some of the issues related to the Key Questions and presents graphs that clearly summarize some of the data and add references for some the information noted below. In addition, the HTA reviewers may find many of the questions are answered at Up-To-Date, an independent service that reviews medical diagnoses and treatments from all of medicine.

1. a. What is the evidence of a reliable and valid case definition for treatment-resistant depression (TRD)?

There is not one standard definition of treatment-resistance and is often used interchangeably with the term "medication-resistance". Medication-resistance often refers to patients with depression who have failed to respond to at least two adequate courses of antidepressant medication. In the STAR*D study in which sequential antidepressant medications were administered, the probability of responding to an antidepressant trial decreased with the number of previous failed trials. For example, the remission rate after an adequate antidepressant of citalopram and a group of depressed patients who had never been treated with a depressant medication was 37%. Among those who failed to respond to citalopram, the next antidepressant trial resulted in a 31% remission rate. Among those who failed the second trial, the next antidepressant trial resulted in only a 14% remission. In those who failed three antidepressant trials, the remission rate was 13%.1

b. Is there a reliable and valid definition of clinically meaningful improvement for depression and function for patients treated for TRD?

In the literature concerning major depressive disorder, response and remission are the two major categories that have been used to measure improvement. “Response” has typically been defined as at least a 50% reduction in the depression rating scale. The most commonly used depression ratings are the Hamilton Depression Rating Scale and the Montgomery-Asberg Depression Rating Scale (MADRS). “Remission” is typically defined as a Hamilton Depression Rating of less than eight or a MADRS of less than 10.

2.a. Are the following nonpharmacologic treatments effective for TRD?

• Electroconvulsive therapy (ECT)

ECT is the most effective treatment for severe depression. Well-controlled studies have been done using simulated ECT showing that ECT is effective. ECT has been found to be superior when compared to antidepressant medications. ECT results in a greater percentage of response and remission and a greater degree of response. The effectiveness of ECT has been reviewed in more depth elsewhere.2,4 In addition, the FDA has reviewed the efficacy of ECT. (FDA Executive Summary: Prepared for the January 27-28, 2011 meeting of the Neurological Devices Panel. Meeting to Discuss the Classification of Electroconvulsive Therapy Devices
The remission rates with ECT do not significantly decrease with increasing medication resistance according to one study. In patients with no previous failed antidepressant trials, the remission rate with ECT is 71%. In those who have failed one adequate antidepressant trial, the remission rate is 65%. In those who failed two antidepressant trials, the remission rate is 63%. In those who failed 3 or more antidepressant trials the remission rate is 60%. According to another study, failure to respond to an antidepressant lowers the ECT response rate from 91% to 63%. Even in the medication-resistant population, ECT has a better outcome than would be expect from yet another trial of an antidepressant.

- Repetitive transcranial magnetic stimulation (rTMS)
  rTMS has been found to be effective in patients with medication-resistance who have failed one antidepressant trial and was approved by the FDA for this group of patients. In the clinical trials, the response and remission rates of those who had more than one antidepressant trial were no greater than the sham stimulation. However, the clinical studies of rTMS, patients were required to discontinue their current antidepressant medication. This may have underestimated the potential value of rTMS in treating patients with medication resistance. rTMS is usually used now as an augmentation strategy. In this clinical setting, rTMS has been found to be associated with significant response and remission rates and improves the quality of life. New research in TMS may lead to even better efficacy.

- Deep brain stimulation (DBS)
  DBS is typically reserved for patients who have failed multiple antidepressant trials. Most studies have not been controlled trials. In a trial that studied depressed patients who had failed at least 4 antidepressant trials, the remission rates were about 20% over the subsequent year and the response rates were about 50% over the subsequent year. From the STAR*D study, we know that these improvements are much better than would have been expected in this population.

- Transcranial direct current stimulation (tDCS)
  There have been promising studies of tDCS. However, the effectiveness in medication resistant depression is not clear. Because of the apparent good side effect profile of key DCS, this approach could be considered even in non-medication resistant depressed patients.

b. Does the effectiveness of these treatments vary according to treatment intensity, duration of treatment, use in an augmentation versus switch strategy, or any other variation in the manner in which TRD treatment was administered?

ECT- The major development in ECT over the past 10 years has been the introduction of ultra-brief right unilateral ECT. This technique has been shown to be as effective as by temporal ECT with much less memory disturbance. The right unilateral technique is intensity dependent. Patients treated with right unilateral ECT at a stimulus intensity of six times the seizure threshold are more likely to remit than those treated at seizure threshold. Some studies have shown this treatment to be as effective as bitemporal ECT. The average duration of treatment is about three weeks. Typically three ECT sessions are given per week. The average number of sessions is eight or nine. ECT is
very effective even when not given with an antidepressant medication. However, the addition of an antidepressant medication may augment the ECT response.

rTMS- The effectiveness of rTMS increases with the number of rTMS sessions. It may be necessary to have as many as 30 TMS sessions. Initial studies of TMS were probably under-dosed. Many of those studies looked at the effectiveness of only 10 or 15 TMS sessions. More recent data indicate that by increasing the number of sessions or the number of pulses per session can significantly increase the effectiveness of TMS. Initial studies of TMS required that patients discontinue their current antidepressant medication. In practice TMS is now primarily used as an augmentation strategy for antidepressant medication that has either been not effective or only partially effective. The response and remission rates in these studies are clearly greater than in the studies of rTMS that required discontinuation of the antidepressant medication. See the powerpoint presentation for further references.

DBS- I’ve not researched the literature on these issues in the brain stimulation.

tDCS- I’ve not researched the literature on these issues in direct current stimulation.

3. What adverse events, including withdrawal from treatment, are associated with nonpharmacologic treatments for TRD?

ECT- The potential side effects of electroconvulsive therapy have been well studied. The side effects of been summarized well in Up-To-Date. Patients may experience a temporary memory disturbance. As noted above, this memory disturbance has been markedly decreased with the introduction of the ultra-brief right unilatral technique. While memory disturbance can occur with ECT, the cognitive problems associated with depression, should not be underestimated. Because ECT is very effective in treating depression, on average patients experience an improvement in neurocognitive functioning. Patients receiving ECT may experience a headache, nausea, muscle soreness, and temporary disorientation following an ECT session. The mortality rate from ECT is very low, approximately one in 10,000 or one and 20,000 treatments. Because depression is associated with increased mortality, ECT is associated with a reduction in mortality rates in depressed populations compared to depressed patients who did not receive ECT.15

rTMS- rTMS has a very good side effect profile that is described in the powerpoint.

DBS- The side effects are described well in Up-To-Date.

tDCS- I am not familiar with the side effects of tDCS.

4. Does the effectiveness of nonpharmacologic treatments for TRD vary by subpopulation defined by such factors as: age, race/ethnicity, gender, disease severity, disease duration, depression diagnosis (unipolar or bipolar depression), symptom type (e.g., psychotic, postpartum), comorbidities, or number and type of prior treatments (including other nonpharmacologic treatments)?

ECT- ECT has been found effective across a wide range of subpopulations16. ECT may be more effective in older depressed patients and in depressed patients with psychotic
features compared to non-psychotic depressed patients. ECT is equally effective in unipolar and bipolar depressed patients. As noted above, some studies show that medication resistance significantly worsens the response to ECT; others do not.

rTMS- rTMS appears be effective primarily in non-psychotic depressed patients.

DBS- I am not familiar with the efficacy of DBS in subpopulations.

tDCS- I am not familiar with the efficacy of tDCS in subpopulations.

5. What are the cost implications and cost-effectiveness of nonpharmacologic therapies for TRD?

ECT - Although ECT is more expensive than an antidepressant medication, ECT is cost-effective for selected patients. Because ECT is more effective and works more quickly than antidepressant medication, ECT can decrease the duration of hospitalization and markedly lower those costs. For depressed outpatients, ECT’s effectiveness can decrease the number of antidepressant trials and the associated outpatient visits and medication costs. In addition, maintenance ECT is able to lower the risk of rehospitalization rates and lower costs.\(^{17}\) Cost-effectiveness should take into account the degree of medication-resistance of the patient population.\(^{18}\) Increasing medication resistance increases the health care costs. Although the initial costs of ECT are greater than for rTMS, ECT was found more cost-effective than rTMS in one British study.\(^ {19}\)

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Personal Perspective: I retired from the University of Washington as Professor Emeritus in 2012 and am now in private practice. I administer ECT to about 2 patients per month. As a young doctor, I did research on ECT that found that ECT was more effective than antidepressant medication\(^ {20}\) and that ECT lowers the mortality rate in depression compared to patients with depression not treated with ECT\(^ {15}\). I was Director of the Inpatient Psychiatry Service for most of the years from 1980 to 2012 and Director of the ECT Service at Harborview Medical Center from 1980 to 2012. It was very gratifying to see patients respond well to ECT. However, it was also a challenge to provide this service to the Medicaid population in Western Washington. Over the last 7 years, Harborview has been the only hospital in Western Washington to offer ECT to Medicaid patients. I had heard from other clinicians that the primary reason that other hospitals stopped this service was because of the poor reimbursement for ECT from Medicaid. Harborview Medical Center was probably offering ECT to Medicare patients at a financial loss. Now, with limited bed availability at Harborview, many patients who would benefit from ECT do not have ECT available to them. It is unfortunate that Medicaid patients do not have access to the most effective treatment for major depression.
I have also done research on transcranial magnetic stimulation for 16 years beginning in 1996. It is clear that TMS more effective than a sham control condition. It is also clear that TMS has a better side effect profile than ECT. However, TMS has not yet achieved the efficacy of ECT. It is possible that more sessions or more pulses or a different type of TMS stimulation might allow greater efficacy, but so far ECT is more efficacious. TMS appears to be as effective as antidepressant medications for medication-resistant depressed patients.

Thank you for the opportunity to comment on these treatments. If I can help in any way, please feel free to contact me.

Sincerely yours,

David H. Avery, M.D.
Professor Emeritus
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Psychiatric Medicine Associates
Cell 206 607 7208
Fax 206 386 3123
averydh225@gmail.com


1.
Brain Stimulation Approaches To Treatment-Resistant Depression

David Avery, M.D.
Psychiatric Medicine Associates
Professor Emeritus
Department of Psychiatry and Behavioral Sciences
University of Washington

Outline

• Electroconvulsive Therapy (ECT)
• Transcranial Magnetic Stimulation (TMS)
• Transcranial Direct Current Stimulation (tDCS)
• Pulsed Electromagnetic Field Therapy (PEMF)
• Transcranial Cranial Electrical Stimulation (tCES)
• Vagus Nerve Stimulation (VNS)
• Deep Brain Stimulation (DBS)
Update on ECT

- Efficacy
  - Right Unilateral
- Administration
  - Ultrabrief Pulse
- Adverse effects
  - Memory
- Does ECT alter brain structure?
- Proposed mechanisms of action
  - Neuroplasticity

STAR-D Remission Rates Across All 4 Levels

Remission Definition:
HAMD-17 ≤7

Mono = single medication regimen; Augm = combination medication treatment; 
1Trivedi MH et al. (2006), Am J Psychiatry 163:28-40; 
4Nierenberg AA et al. (2006), Am J Psychiatry 163:1519-1530; 
5Fava M et al. (2006), Am J Psychiatry 163:1161-1172; 
6McGrath PJ et al. (2006), Am J Psychiatry 163(9):1531-1541
Medication-Resistant Depression
Not Uncommon.

- Major Depressive Disorder – 7% prevalence in one year. (Kessler, 2005)
- 33% do not respond to multiple adequate antidepressant trials. (STAR*D, Rush, 2006)
- About 2% of population has Medication-Resistant Depression.

Medication-Resistant Depression
Associated with:

- Greater risk of suicide (Fawcett, 2001)
- Increased mortality (Carney, 2009)
- Functional impairment (Miller, 1998)
- Increased utilization of health care resources (Crown, 2002)
ECT is the Most Effective Treatment for Major Depression

- Greater Degree of Response
  - Effect size for ECT is 0.91 (UK Review Group, 2003)
  - Effect size for Antidepressants is 0.39-0.49 (Khan; Berman, 2007)
- Greater Remission and Response Rates
- Faster Response

ECT vs Simulated ECT (UK Review Group, 2003)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of participants</th>
<th>Standardised effect size (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Wilson 1963</td>
<td>12</td>
<td>-1.078 (-2.289 to 0.133)</td>
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<tr>
<td>West 1961</td>
<td>25</td>
<td>-1.255 (-2.170 to -0.341)</td>
</tr>
<tr>
<td>Lambourn 1978</td>
<td>40</td>
<td>-0.170 (-0.940 to 0.600)</td>
</tr>
<tr>
<td>Freeman 1978</td>
<td>40</td>
<td>-0.629 (-1.204 to 0.006)</td>
</tr>
<tr>
<td>Gregory 1985</td>
<td>69</td>
<td>-1.418 (-2.012 to -0.824)</td>
</tr>
<tr>
<td>Johnstone 1980</td>
<td>70</td>
<td>-0.739 (-1.253 to -0.224)</td>
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<tr>
<td>Pooled fixed effects</td>
<td></td>
<td>-0.911 (-1.180 to -0.645)</td>
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<tr>
<td>Pooled random effects</td>
<td></td>
<td>-0.908 (-1.270 to -0.537)</td>
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Figure 1: Effect of ECT versus simulated ECT on depressive symptoms
### ECT vs Pharmacotherapy (UK Review Group, 2003)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Participants</th>
<th>Standardized Effect Size (95% CI)</th>
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<tr>
<td>Steiner 1978&lt;sup&gt;11&lt;/sup&gt;</td>
<td>13</td>
<td>-0.369 (-0.840 to 1.578)</td>
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<tr>
<td>Wilson 1983&lt;sup&gt;15&lt;/sup&gt;</td>
<td>12</td>
<td>-0.513 (-1.663 to 0.637)</td>
</tr>
<tr>
<td>Davidson 1974&lt;sup&gt;17&lt;/sup&gt;</td>
<td>19</td>
<td>-0.289 (-2.469 to 0.890)</td>
</tr>
<tr>
<td>McDermott 1986&lt;sup&gt;18&lt;/sup&gt;</td>
<td>22</td>
<td>-0.501 (-1.813 to 0.812)</td>
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<tr>
<td>Garner 1992&lt;sup&gt;13&lt;/sup&gt;</td>
<td>32</td>
<td>1.267 (0.406 to 2.109)</td>
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<td>MetSweeney 1975&lt;sup&gt;15&lt;/sup&gt;</td>
<td>27</td>
<td>-0.714 (-1.492 to 0.065)</td>
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<tr>
<td>Osnos 1986&lt;sup&gt;17&lt;/sup&gt;</td>
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<td>-0.196 (-0.629 to 0.234)</td>
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<tr>
<td>Jensen-Acrossen 2002&lt;sup&gt;12&lt;/sup&gt;</td>
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<td>Pickerts 1994&lt;sup&gt;17&lt;/sup&gt;</td>
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<td>Harrington 1974&lt;sup&gt;14&lt;/sup&gt;</td>
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<td>Medical Research Council 1965&lt;sup&gt;16&lt;/sup&gt;</td>
<td>204</td>
<td>-0.599 (-0.883 to -0.314)</td>
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<tr>
<td>Greenblatt 1964&lt;sup&gt;17&lt;/sup&gt;</td>
<td>242</td>
<td>-1.683 (-2.520 to -0.846)</td>
</tr>
</tbody>
</table>

**Pooled fixed effects**: -0.010 (-1.170 to -0.050)

**Pooled random effects**: -0.003 (-1.290 to -0.066)

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### Bitemporal vs Unilateral ECT (UK Review Group, 2003)

<table>
<thead>
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<th>Study</th>
<th>Number of Participants</th>
<th>Standardized Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arens 1995&lt;sup&gt;H&lt;/sup&gt;</td>
<td>10</td>
<td>0.317 (0.744 to 0.347)</td>
</tr>
<tr>
<td>Neave 1988&lt;sup&gt;21&lt;/sup&gt;</td>
<td>24</td>
<td>0.296 (0.744 to 0.507)</td>
</tr>
<tr>
<td>Root 1989&lt;sup&gt;2&lt;/sup&gt;</td>
<td>33</td>
<td>-0.235 (-0.571 to 0.084)</td>
</tr>
<tr>
<td>Areanas 1978&lt;sup&gt;21&lt;/sup&gt;</td>
<td>30</td>
<td>0.672 (0.479 to 0.865)</td>
</tr>
<tr>
<td>Cooper 1977&lt;sup&gt;2&lt;/sup&gt;</td>
<td>30</td>
<td>0.042 (0.108 to 0.478)</td>
</tr>
<tr>
<td>Osmo 1977&lt;sup&gt;21&lt;/sup&gt;</td>
<td>36</td>
<td>-0.157 (0.613 to 0.986)</td>
</tr>
<tr>
<td>Teply 1998&lt;sup&gt;17&lt;/sup&gt;</td>
<td>17</td>
<td>-0.952 (-1.846 to -0.059)</td>
</tr>
<tr>
<td>Areanas 1990&lt;sup&gt;21&lt;/sup&gt;</td>
<td>36</td>
<td>0.505 (-1.659 to 2.669)</td>
</tr>
<tr>
<td>Osmo 1983&lt;sup&gt;21&lt;/sup&gt;</td>
<td>44</td>
<td>0.556 (0.470 to 0.633)</td>
</tr>
<tr>
<td>Lees 1983&lt;sup&gt;21&lt;/sup&gt;</td>
<td>40</td>
<td>0.350 (0.583 to 0.413)</td>
</tr>
<tr>
<td>Osmo 1990&lt;sup&gt;21&lt;/sup&gt;</td>
<td>40</td>
<td>0.515 (-1.613 to 2.543)</td>
</tr>
<tr>
<td>Osmo 1992&lt;sup&gt;21&lt;/sup&gt;</td>
<td>45</td>
<td>0.086 (-1.767 to 0.098)</td>
</tr>
<tr>
<td>Hanshaw 1985&lt;sup&gt;21&lt;/sup&gt;</td>
<td>48</td>
<td>-0.180 (-0.703 to 0.343)</td>
</tr>
<tr>
<td>Areanas 1998&lt;sup&gt;21&lt;/sup&gt;</td>
<td>70</td>
<td>0.658 (-1.615 to 2.921)</td>
</tr>
<tr>
<td>Inlay 1988&lt;sup&gt;21&lt;/sup&gt;</td>
<td>72</td>
<td>-0.072 (-1.562 to 1.419)</td>
</tr>
<tr>
<td>Savard 1987&lt;sup&gt;21&lt;/sup&gt;</td>
<td>52</td>
<td>0.395 (0.140 to 0.649)</td>
</tr>
<tr>
<td>Math 1988&lt;sup&gt;21&lt;/sup&gt;</td>
<td>52</td>
<td>-0.360 (0.340 to 0.020)</td>
</tr>
<tr>
<td>Unordered 1989&lt;sup&gt;18&lt;/sup&gt;</td>
<td>33</td>
<td>-0.382 (0.703 to 0.964)</td>
</tr>
<tr>
<td>Steble 1991&lt;sup&gt;21&lt;/sup&gt;</td>
<td>39</td>
<td>-0.328 (-0.719 to 0.063)</td>
</tr>
<tr>
<td>Lack 1999&lt;sup&gt;21&lt;/sup&gt;</td>
<td>34</td>
<td>-0.303 (-1.802 to 0.196)</td>
</tr>
<tr>
<td>Savard 1993&lt;sup&gt;21&lt;/sup&gt;</td>
<td>100</td>
<td>0.594 (0.195 to 0.993)</td>
</tr>
<tr>
<td>Intergen 1993&lt;sup&gt;21&lt;/sup&gt;</td>
<td>127</td>
<td>0.405 (-0.016 to 0.826)</td>
</tr>
</tbody>
</table>

**Pooled fixed effects**: -0.023 (-0.446 to 0.096)

**Pooled random effects**: -0.023 (-0.466 to 0.018)
### 1X per week ECT vs 3X per week ECT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of participants</th>
<th>Standardised effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kellner 1992</td>
<td>11</td>
<td>0.564 (-0.626 to 1.344)</td>
</tr>
<tr>
<td>Janakriamanah 1994</td>
<td>40</td>
<td>0.340 (0.287 to 1.593)</td>
</tr>
<tr>
<td>Pooled fixed effects</td>
<td></td>
<td>0.861 (0.361 to 1.376)</td>
</tr>
<tr>
<td>Pooled random effects</td>
<td></td>
<td>0.552 (-0.389 to 1.006)</td>
</tr>
</tbody>
</table>

### 2X per week ECT vs 3X per week ECT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of participants</th>
<th>Standardised effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gangadhar 1997</td>
<td>30</td>
<td>0.239 (-1.013 to 0.485)</td>
</tr>
<tr>
<td>Shapiro 1998</td>
<td>31</td>
<td>0.323 (-0.545 to 0.881)</td>
</tr>
<tr>
<td>Vorvig 1999</td>
<td>40</td>
<td>0.888 (-1.330 to 0.246)</td>
</tr>
<tr>
<td>Laver 1993</td>
<td>52</td>
<td>0.049 (-0.523 to 0.621)</td>
</tr>
<tr>
<td>Pooled fixed effects</td>
<td></td>
<td>0.938 (-0.629 to 0.416)</td>
</tr>
<tr>
<td>Pooled random effects</td>
<td></td>
<td>0.209 (-0.759 to 1.180)</td>
</tr>
</tbody>
</table>

### Higher Dose ECT vs Lower Dose ECT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of participants</th>
<th>Standardised effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCall 1995</td>
<td>22</td>
<td>0.829 (-0.042 to 1.700)</td>
</tr>
<tr>
<td>Warren 1998</td>
<td>23</td>
<td>1.218 (0.463 to 1.974)</td>
</tr>
<tr>
<td>Janakriamanah 1984</td>
<td>40</td>
<td>0.273 (-0.349 to 0.886)</td>
</tr>
<tr>
<td>McCall 2000</td>
<td>72</td>
<td>0.389 (-0.078 to 0.855)</td>
</tr>
<tr>
<td>Sackeim 2000</td>
<td>80</td>
<td>0.368 (-0.141 to 0.877)</td>
</tr>
<tr>
<td>Sackeim 1993</td>
<td>100</td>
<td>0.650 (0.239 to 1.061)</td>
</tr>
<tr>
<td>Pooled fixed effects</td>
<td></td>
<td>0.571 (0.352 to 0.790)</td>
</tr>
<tr>
<td>Pooled random effects</td>
<td></td>
<td>0.575 (0.329 to 0.829)</td>
</tr>
</tbody>
</table>

*Other trials not included: Keystall 1996.*
ECT is equally effective in treating unipolar depression and bipolar depression.

Dierckx et al, 2012

Relapse Rates following Remission with ECT During the 6-Month Followup

- With Placebo, 84%.
- With Nortriptyline, 60%
- With Nortriptyline plus lithium, 39%

Sackheim, 2001

The relapse rates from this study from the 1990s are higher than those seen in the 1960s. Probably patients with higher levels of medication-resistance were being treated with ECT in the 1990s.

Continuation ECT vs Continuation Pharmacotherapy

Kellner 2006

Figure 2. Kaplan-Meier curves showing proportion of patients who remained in disease remission (not disease relapse) during the continuation phase (phase 2). Log-rank test comparing distributions of time to relapse for C-ECT vs C-Pharm: $\chi^2=0.30; P=.59$. C-ECT indicates continuation electroconvulsive therapy; C-Pharm, combination of lithium carbonate plus nortriptyline hydrochloride.
**Treatment Responsive Disorders**

- Major Depressive Illness with or without psychotic features
- Bipolar, depressed
- Bipolar, manic
- Schizoaffective Disorder
- Schizophrenia - acute onset, confusion
- Catatonia
- Parkinson’s Disease (bradykinesia, tremor, rigidity, gait disturbance, postural instability)
- Chronic pain associated with Major Depression

**A Case-Matching Study of the Analgesic Properties of ECT**

- Inpatients with Major Depression and Chronic Pain- Johns Hopkins University
- Case-Matched for age, gender, admission date, psychiatric diagnosis, and pain syndrome.
- N=25 in each group
- Depression ratings: 55.9% reduction with ECT, 40.5% with antidepressants.
- Analgesic effect of ECT present even when controlling for antidepressant effect.

Wasan et al, 2004
A Case-Matching Study of the Analgesic Properties of ECT

Predictors of Response

Positive
- Previous history of response
- Psychomotor retardation
- Psychotic Features
- Positive family hx
- Autonomous to circumstance

Negative
- Chronicity
- Reactive
- Unstable relationships
- Denial
- Axis II
- Medication Resistance?
Failure of an adequate trial of hetercyclics (but not SSRIs) was associated with a poor response to Unilateral ECT (Prudic et al, 1996).

<table>
<thead>
<tr>
<th>Previous Antidepressant Treatment</th>
<th>% Response to ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never adequate trial</td>
<td>91%</td>
</tr>
<tr>
<td>Failed adequate trial</td>
<td>63%</td>
</tr>
</tbody>
</table>

The remission rates with bitemporal ECT (N=216) do not significantly decrease with increasing medication resistance.

(Rasmussen, et al. 2007)
**Star-D Remission Rates-4**

Overall remission rate (QIDS-SR16) = 67%

![Graph showing remission rates across steps](image)

(Rush, et al. 2006)

The remission rates with bitemporal ECT (N=216) do not significantly decrease with increasing medication resistance.

![Bar graph showing remission rates](image)

(Rasmussen, et al. 2007)
Pre-ECT Workup

- History
- Physical Exam
- Electrolytes
- Creatinine
- CBC
- Liver function tests
- Urinalysis
- EKG

Consider

- Brain CT
- EEG
- Spine X-Ray
- Chest X-ray

Relative Contradictions to ECT

- Intracranial neoplasm
- Recent cerebral vascular accident
- Subdural hematoma
- Recent myocardial infarction
- Angina
- Congestive heart failure
- Acute or chronic respiratory disease
Administration of ECT

- NPO
- Hyperoxygenation
- Short acting anesthetic – Etomidate or Methohexital
- Succinylchlorine + blood pressure cuff techniques

<table>
<thead>
<tr>
<th>Consider</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Atropine</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Labetalol</td>
<td>esp. Benzodiazapines</td>
</tr>
<tr>
<td>Esmolol</td>
<td>(Consider Zolpidem for sleep)</td>
</tr>
</tbody>
</table>

Should an Antidepressant Medication be given with ECT?

- ECT response rates significantly better with concomitant antidepressant (venlafaxine or nortriptyline) compared with placebo.
Studies Comparing Bilateral and Unilateral ECT

- Bilateral better than Unilateral 13
- Bilateral equal to Unilateral 14
- Unilateral better than Bilateral 2

Right Unilateral ECT at 6X seizure threshold is as effective as Bilateral ECT with significantly less cognitive disturbance.

<table>
<thead>
<tr>
<th>ECT</th>
<th>Remission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral</td>
<td>65%</td>
</tr>
<tr>
<td>RUL-6X</td>
<td>60%</td>
</tr>
<tr>
<td>RUL-2.5X</td>
<td>30%</td>
</tr>
<tr>
<td>RUL-1.5X</td>
<td>35%</td>
</tr>
</tbody>
</table>

Sackeim et al, 2000
High Dose Right Unilateral ECT as Efficacious as Bitemporal ECT with Less Cognitive Disturbance

- Abrams et al, 1991 (n=38)
- Sackeim et al, 1993 (n=96)
- Sackeim et al, 2000 (n=80)

Right Unilateral ECT Efficacy Increases with Intensity

- Right Unilateral (RUL) ECT given at seizure threshold is significantly less effective than RUL ECT given at 2.25 to 12.6 times seizure threshold

- Cognitive disturbance also increases with intensity

McCall et al, 2000
Pulse and sine wave comparison. Energy = area under curve

Waveform characteristics of sine wave and square wave stimulus generators under typical operating conditions with standard patient impedances.

Brief Pulse Stimulus Parameters

Charge: (pulse width) x (twice frequency) x (duration) x (peak current) [milliampere seconds]

Energy: (charge) x (peak current) x (dynamic impedance) / 1000 [Joules]
Ultrabrief Pulsewidth ECT

- Ultrabrief Pulsewidth: 0.25-0.3 msec
- More efficient induction of seizure than 1.0 msec pulsewidth
- > 1.0 msec PW falls within the refractory period of the neurons.
- Able to induce seizure with 1-10% of machine output with ultrabrief compared to 30-40% with 1.5 ms pulsewidth.
- Data from Columbia shows that right unilateral ultrabrief at 6x seizure threshold is as effective as bitemporal with less memory disturbance.

Sackeim et al., Brain Stimulation, 2008

Ultrabrief ECT Study

- 90 depressed subjects randomized to:
  - Brief Pulse (1.5 msec) - Right Unilateral 6X seizure threshold
  - Ultrabrief Pulse (.30 msec) - Right Unilateral 6X seizure threshold
  - Brief Pulse (1.5 msec) – Bitemporal 2.5 x seizure threshold.
  - Ultrabrief Pulse (.30 msec) – Bitemporal 2.5 x seizure threshold.
Remission Rates One-Week Post ECT

Sackeim et al, 2008

Amnesia for Autobiographical Memory Post-ECT

Sackeim et al, 2008
Starting with Ultrabrief RUL (.3pw) vs Starting with Bitemporal (1.0pw)

- Retrospective Chart Review
- Starting with Ultrabrief RUL, 46% switched to Bitemporal ECT. Mean # of sessions 9.4
- Starting with Bitemporal. Mean # of sessions = 7.7.
- An Ultrabrief RUL session may be less effective than a Bitemporal session.

McCormick, 2009

Ketamine Augmentation of ECT

Notes: RUL indicates right unilateral (N = 22); RUL UB, right unilateral ultra brief (N = 78); Ketamine with RUL UB (N = 7); Placebo (N = 8).
The following slides show a typical two lead EEG during an ECT treatment.

- Recruitment
- Tonic phase of seizure
- Clonic phase of seizure
Clinical Response to ECT associated with some EEG characteristics:

- Greater Post-ictal Suppression
- Greater Left-Right Coherence
- Increased delta and theta in the prefrontal regions.
- Seizure duration a weak predictor.
**Adverse Effects to ECT**

- Death – 1/10,000 to 1/20,000
- Post-Ictal Confusion
- Memory Disturbance
- Headache
- Muscle aches
- Mania

**Memory Disturbance with ECT**

<table>
<thead>
<tr>
<th>Months</th>
<th>Before ECT</th>
<th>ECT</th>
<th>After ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

- Retrograde Amnesia
- Anterograde Amnesia
Bitemporal ECT has some persistent retrograde amnesia at 2 month follow-up

- Nondepressed control group
- Greater for impersonal memories than for personal
- RUL-2.5x threshold had much less memory disturbance than bilateral

Lisanby et al, 2000

Right Unilateral ECT at 6X seizure threshold has much less cognitive disturbance than Bilateral ECT

- Anterograde Memory
- Retrograde memory
- Mini-mental state
- Paired Words

Sackeim et al, 2000
AGE-RELATED COGNITIVE EFFECTS OF ECT AND ECT-INDUCED MOOD IMPROVEMENT IN DEPRESSIVE PATIENTS

P. R. Bosboom, M.Sc., and J. B. Deijen, Ph.D.*

This explorative study investigated the interaction between electroconvulsive therapy (ECT) treatment-effect, reduced depression, and neuropsychological outcome in relation to age. Follow-up neuropsychological assessment was conducted with depressive patients treated with ECT. From a potential sample of 45 patients, the neuropsychological measures (pre-ECT; three times post-ECT, up to 12 months) and clinical data from the remaining 21 patients who completed all assessments were evaluated (mean age = 56.76; SD = 14.12; range, 33–79). ECT resulted in a decrease in the depression scores. A distinct impact of ECT and depression decrease on cognitive domains was found. Depression alleviation was mainly associated with improvement in cognitive domains such as memory, information processing, and executive function. ECT improved cognitive domains such as information processing and perception. Short-term cognitive improvement was greater in older patients but showed an increase similar to that at long-term follow-up in younger patients (<60). Current findings provide evidence that ECT may improve cognitive functioning in undemented elderly, which has strong clinical relevance concerning the use of ECT.


Cognition functions often improve with ECT

<table>
<thead>
<tr>
<th>Cognitive test variable</th>
<th>1 and 2&lt;sup&gt;1&lt;/sup&gt;</th>
<th>2 and 3</th>
<th>3 and 4</th>
<th>1 and 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without covariate</td>
<td>With covariate</td>
<td>Without covariate</td>
<td>Without covariate</td>
</tr>
<tr>
<td>WMS Paired Associates</td>
<td>0.23</td>
<td>0.029</td>
<td>0.23</td>
<td>0.017</td>
</tr>
<tr>
<td>H-Word List</td>
<td>0.23</td>
<td>0.029</td>
<td>0.23</td>
<td>0.017</td>
</tr>
<tr>
<td>BVMT Correct Responses</td>
<td>0.30</td>
<td>0.046</td>
<td>0.27</td>
<td>0.011</td>
</tr>
<tr>
<td>WMS Visual Reproduction</td>
<td>0.27</td>
<td>0.017</td>
<td>0.28</td>
<td>0.019</td>
</tr>
<tr>
<td>WMS Orientation</td>
<td>0.30</td>
<td>0.046</td>
<td>0.27</td>
<td>0.011</td>
</tr>
<tr>
<td>MOB Semantic Recent</td>
<td>0.30</td>
<td>0.046</td>
<td>0.27</td>
<td>0.011</td>
</tr>
<tr>
<td>GTT Word Matrices</td>
<td>0.38</td>
<td>0.007</td>
<td>0.53</td>
<td>0.017</td>
</tr>
<tr>
<td>Stroop Card I speed</td>
<td>0.24</td>
<td>0.037</td>
<td>0.26</td>
<td>0.047</td>
</tr>
<tr>
<td>Stroop Card II factors</td>
<td>0.28</td>
<td>0.017</td>
<td>0.28</td>
<td>0.024</td>
</tr>
<tr>
<td>WMS Digt Symbol</td>
<td>0.30</td>
<td>0.046</td>
<td>0.27</td>
<td>0.011</td>
</tr>
<tr>
<td>WMS Mental Control</td>
<td>0.30</td>
<td>0.046</td>
<td>0.27</td>
<td>0.011</td>
</tr>
<tr>
<td>GTT IQ</td>
<td>0.65</td>
<td>0.005</td>
<td>0.65</td>
<td>0.005</td>
</tr>
<tr>
<td>GTT Incomplete Pictures</td>
<td>0.65</td>
<td>0.005</td>
<td>0.65</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*See text for description of tests.
1Session 1, one week before ECT index; session 2, one week after ECT index; session 3, 6 months after session 1; 6 months after session 3.

Depression and Anxiety DOI 10.1002/an

Bosboom, 2006
Session 1, one week before ECT index;
Session 2, one week after ECT index;
Session 3, 6 months after session 2;
Session 4, 12 months after session 2.

Bosboom, 2006

Patients given more than 100 Lifetime ECT vs. Matched Non-ECT Patients

No differences in cognition scores:

• Mini-Mental Status

• Buschke Selective Reminding Test

• Subjective Memory Questionnaire:
  Events long ago, Events a few minutes ago, Names and faces of people, Events a month from now, Global.

Case Reports of Memory Not Returning to Normal; May Be Due to Any of Several Factors

- A sensitization to normal forgetting following the transient organic amnesia that often accompanies the ECT treatment course
- Residual and/or recurrent symptoms related to the condition for which ECT was used.
- Concurrent medication use or substance abuse.
- Comorbid Brain Disease
- A Conversion type of syndrome
- Psychological reinforcemnt of transient organic losses (secondary gain)
- An idiosyncratic neurobiological effect. Mankad, 2010

Does ECT Alter Brain Structure?

Animal Studies

- Qualitative analyses using perfusion fixation
- Neuronal counting
- Electrical amperage – 1,800 mA
- Thermal effects
- Blood brain barrier changes
- Protein synthesis
- DNA single strand break
Does ECT Alter Brain Structure?

Human Studies

- Computerized axial tomography
- Magnetic resonance imaging
- Paired Words
- Autopsies of ECT patients
- Autopsies of epilepsy patients

“There is No Credible Evidence That ECT Causes Structural Brain Damage”

Devanand et al,
Amer J of Psychiatry 1994, 151:957-970
### Proposed Mechanisms of Action ECT

- Introjected anger
- Memory disturbance
- Increased NE, serotonin, Brain-Derived Neurotrophic Factor (BDNF), GABA release
- Down regulation of beta-adrenergic receptors
- Endogenous anticonvulsant Production
- Resynchronizes the “Body Clocks” (Circadian, Ultradian such as 90 minute REM-NREM cycle, or EEG coherence)
  - Analogous to cardiac shock

### Good ECT Response Associated with:

- Post-ictal suppression of EEG.
- Left-Right Coherence (synchrony) of EEG during the ECT
- Increased delta and theta in the prefrontal regions in post-ictal period.
ECT Seizure Threshold

- Males higher than females.
- Depressed higher than manic.
- Increases with age.
- Increases as the Number of ECT Treatment Increases
- Increases are Related to the Degree of Response to ECT
- Greater Increases with Bilateral than Unilateral ECT
GABA Hypothesis of Depression

- GABA decreases with stress
- GABA decreased in CSF of Depressed Patients - 7 studies
- GABA decreased in plasma of depressed patients
- GABA decreased in magnetic resonance spectroscopy in Depressed patients
- GABA increases functional connectivity in EEG
- ECT increases GABA levels in depressed patients.
- ECT increases GABA-A receptors in depressed patients.

Brain-Derived Neurotrophic Factor (BDNF) Increases with:

- Antidepressant medication (Duman, 1997)
- Electroconvulsive therapy (Duman, 2000)
- Transcranial Magnetic Stimulation (Muller, 2000)
ECT Increases Neurogenesis in Rats

- Compared to sham stimulation, a single ECT increases the number of newborn neuronal cells in the dentate gyrus of the rat (bromodeoxyuridine)
- Sustained survival of cells for at least 3 months
- Increased synaptogenesis (neuronal cells adhesion molecule) following ECT.
- No increase in apoptotic cells even after 10 ECTs

Maben et al, 2000, Jorgenson and Bolwig, 1979
Brain Stimulation Approaches To Treatment-Resistant Depression

David Avery, M.D.
Psychiatric Medicine Associates
Professor Emeritus
Department of Psychiatry and Behavioral Sciences
University of Washington

Outline

• Electroconvulsive Therapy (ECT)
• Transcranial Magnetic Stimulation (TMS)
• Transcranial Direct Current Stimulation (tDCS)
• Pulsed Electromagnetic Field Therapy (PEMF)
• Transcranial Cranial Electrical Stimulation (tCES)
• Vagus Nerve Stimulation (VNS)
• Deep Brain Stimulation (DBS)
Update on ECT

- Efficacy
  - Right Unilateral
- Administration
  - Ultrabrief Pulse
- Adverse effects
  - Memory
- Does ECT alter brain structure?
- Proposed mechanisms of action
  - Neuroplasticity

STAR-D Remission Rates Across All 4 Levels

Remission Definition: HAMD-17 ≤7

Mono = single medication regimen; Augm = combination medication treatment;
Medication-Resistant Depression Not Uncommon.

- Major Depressive Disorder – 7% prevalence in one year. (Kessler, 2005)
- 33% do not respond to multiple adequate antidepressant trials. (STAR*D, Rush, 2006)
- About 2% of population has Medication-Resistant Depression.

Medication-Resistant Depression Associated with:

- Greater risk of suicide (Fawcett, 2001)
- Increased mortality (Carney, 2009)
- Functional impairment (Miller, 1998)
- Increased utilization of health care resources (Crown, 2002)
ECT is the Most Effective Treatment for Major Depression

• Greater Degree of Response
  – Effect size for ECT is 0.91 (UK Review Group, 2003)
  – Effect size for Antidepressants is 0.39-0.49 (Khan; Berman, 2007)

• Greater Remission and Response Rates

• Faster Response

ECT vs Simulated ECT
(UK Review Group, 2003)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of participants</th>
<th>Standardised effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson 196310</td>
<td>12</td>
<td>-1.078 (-2.289 to 0.133)</td>
</tr>
<tr>
<td>West 196111</td>
<td>25</td>
<td>-1.255 (-2.170 to -0.341)</td>
</tr>
<tr>
<td>Lambourn 197853</td>
<td>40</td>
<td>-0.170 (-0.940 to 0.600)</td>
</tr>
<tr>
<td>Freeman 197812</td>
<td>40</td>
<td>-0.629 (-1.264 to 0.006)</td>
</tr>
<tr>
<td>Gregory 198513</td>
<td>69</td>
<td>-1.418 (-2.012 to -0.824)</td>
</tr>
<tr>
<td>Johnstone 198014</td>
<td>70</td>
<td>-0.739 (-1.253 to -0.224)</td>
</tr>
</tbody>
</table>

Pooled fixed effects
Pooled random effects
-0.911 (-1.180 to -0.645)
-0.908 (-1.270 to -0.537)

Figure 1: Effect of ECT versus simulated ECT on depressive symptoms
ECT vs Pharmacotherapy (UK Review Group, 2003)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Participants</th>
<th>Standardised Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson 1963[12]</td>
<td>27</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>McDonald 1966[10]</td>
<td>22</td>
<td>-1.389 (-1.881 to -0.898)</td>
</tr>
<tr>
<td>MetSweeney 1975[13]</td>
<td>27</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Dwan 1966[15]</td>
<td>30</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
</tbody>
</table>
| Bitemporal vs Unilateral ECT (UK Review Group, 2003)

Bitemoral vs Unilateral ECT (UK Review Group, 2003)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Participants</th>
<th>Standardised Effect Size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arone 1992[16]</td>
<td>24</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Varma 1995[17]</td>
<td>24</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Rees 1995[18]</td>
<td>19</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Arone 1994[19]</td>
<td>20</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Conte 1997[20]</td>
<td>20</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Perényi 1997[20]</td>
<td>20</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Taha 1999[21]</td>
<td>17</td>
<td>-1.097 (-1.663 to -0.531)</td>
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<tr>
<td>Arone 1995[22]</td>
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<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>O'Keefe 1995[23]</td>
<td>45</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Lee 1996[24]</td>
<td>40</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Mark 1995[25]</td>
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<td>-1.097 (-1.663 to -0.531)</td>
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<tr>
<td>Gure 1996[26]</td>
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<td>-1.097 (-1.663 to -0.531)</td>
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<tr>
<td>Hare 1995[27]</td>
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<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Arone 1994[28]</td>
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<tr>
<td>Hare 1989[29]</td>
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<tr>
<td>Saito 1986[30]</td>
<td>52</td>
<td>-1.097 (-1.663 to -0.531)</td>
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<tr>
<td>Math 1984[31]</td>
<td>52</td>
<td>-1.097 (-1.663 to -0.531)</td>
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<tr>
<td>Ursula 1980[32]</td>
<td>42</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Sartor 1978[33]</td>
<td>39</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Takahashi 1975[34]</td>
<td>64</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Takahashi 1975[34]</td>
<td>100</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
<tr>
<td>Scripture 1975[34]</td>
<td>127</td>
<td>-1.097 (-1.663 to -0.531)</td>
</tr>
</tbody>
</table>

Pooled fixed effects: -1.097 (-1.663 to -0.531)
Pooled random effects: -1.097 (-1.663 to -0.531)
1X per week ECT vs 3X per week
2X per week ECT vs 3X per week
(UK Review Group, 2003)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of participants</th>
<th>Standardised effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helleur 1992(1)</td>
<td>11</td>
<td>0.864 (-0.526 to 2.214)</td>
</tr>
<tr>
<td>Janakiramaiah 1994(2)</td>
<td>40</td>
<td>0.710 (0.297 to 1.193)</td>
</tr>
<tr>
<td>Pooled fixed effects</td>
<td></td>
<td>0.864 (0.311 to 1.578)</td>
</tr>
<tr>
<td>Pooled random effects</td>
<td></td>
<td>0.862 (-0.389 to 1.059)</td>
</tr>
<tr>
<td>Twice a week vs three times a week</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gangadhar 1993(3)</td>
<td>30</td>
<td>-0.292 (-1.013 to 0.458)</td>
</tr>
<tr>
<td>Shapira 1996(4)</td>
<td>31</td>
<td>0.212 (-0.040 to 0.463)</td>
</tr>
<tr>
<td>Verheg 1996(5)</td>
<td>46</td>
<td>0.058 (-1.520 to 1.246)</td>
</tr>
<tr>
<td>Lever 1992(6)</td>
<td>52</td>
<td>0.046 (-0.022 to 0.092)</td>
</tr>
<tr>
<td>Pooled fixed effects</td>
<td></td>
<td>-0.058 (-0.259 to 0.144)</td>
</tr>
<tr>
<td>Pooled random effects</td>
<td></td>
<td>-0.058 (-0.159 to 0.134)</td>
</tr>
</tbody>
</table>

Figure 6: Effect of frequency of ECT on depressive symptoms

Higher Dose ECT vs Lower Dose ECT
(UK Review Group, 2003)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of participants</th>
<th>Standardised effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCall 1995(7)</td>
<td>22</td>
<td>0.829 (-0.042 to 1.700)</td>
</tr>
<tr>
<td>Warren 1998(8)</td>
<td>23</td>
<td>1.218 (-0.463 to 1.974)</td>
</tr>
<tr>
<td>Janakiramaiah 1984(9)</td>
<td>40</td>
<td>0.273 (-0.349 to 0.896)</td>
</tr>
<tr>
<td>McCall 2000(10)</td>
<td>72</td>
<td>0.389 (-0.078 to 0.855)</td>
</tr>
<tr>
<td>Sackeim 2000(11)</td>
<td>80</td>
<td>0.388 (-0.141 to 0.877)</td>
</tr>
<tr>
<td>Sackeim 1993(12)</td>
<td>100</td>
<td>0.650 (0.239 to 1.061)</td>
</tr>
<tr>
<td>Pooled fixed effects</td>
<td></td>
<td>0.571 (0.352 to 0.790)</td>
</tr>
<tr>
<td>Pooled random effects</td>
<td></td>
<td>0.575 (0.329 to 0.829)</td>
</tr>
</tbody>
</table>

Figure 7: Effect of higher versus lower dose of ECT on depressive symptoms
*Other trials not included: Keydat 1996(7)
ECT is equally effective in treating unipolar depression and bipolar depression. 

Dierckx et al, 2012

![Chart showing odds ratios of response to electroconvulsive therapy in patients with unipolar versus bipolar depression per study, with 95% confidence interval, after natural logarithmic transformation.]

Relapse Rates following Remission with ECT During the 6-Month Followup

- With Placebo, 84%.
- With Nortriptyline, 60%
- With Nortriptyline plus lithium, 39%
  Sackheim, 2001

The relapse rates from this study from the 1990s are higher than those seen in the 1960s. Probably patients with higher levels of medication-resistance were being treated with ECT in the 1990s.
FIGURE 2. Kaplan-Meier function of the cumulative probability of remaining without relapse for patients treated with continuation ECT plus pharmacotherapy versus pharmacotherapy alone in the intention-to-treat sample.

Nordenskjold, 2013

Continuation ECT vs Continuation Pharmacotherapy

Kellner 2006

Figure 2. Kaplan-Meier curves showing proportion of patients who remained in disease remission (not disease relapse) during the continuation phase (phase 2). Log-rank test comparing distributions of time to relapse for C-ECT vs C-Pharm: $\chi^2=0.30; P=.59$. C-ECT indicates continuation electroconvulsive therapy; C-Pharm, combination of lithium carbonate plus nortriptyline hydrochloride.
Treatment Responsive Disorders

- Major Depressive Illness with or without psychotic features
- Bipolar, depressed
- Bipolar, manic
- Schizoaffective Disorder
- Schizophrenia - acute onset, confusion
- Catatonia
- Parkinson’s Disease (bradykinesia, tremor, rigidity, gait disturbance, postural instability)
- Chronic pain associated with Major Depression

A Case-Matching Study of the Analgesic Properties of ECT

- Inpatients with Major Depression and Chronic Pain- Johns Hopkins University
- Case-Matched for age, gender, admission date, psychiatric diagnosis, and pain syndrome.
- N=25 in each group
- Depression ratings: 55.9% reduction with ECT, 40.5% with antidepressants.
- Analgesic effect of ECT present even when controlling for antidepressant effect.

Wasan et al, 2004
A Case-Matching Study of the Analgesic Properties of ECT

Predictors of Response

Positive
- Previous history of response
- Psychomotor retardation
- Psychotic Features
- Positive family hx
- Autonomous to circumstance

Negative
- Chronicity
- Reactive
- Unstable relationships
- Denial
- Axis II
- Medication Resistance?
Failure of an adequate trial of hetercyclics (but not SSRIs) was associated with a poor response to Unilateral ECT (Prudic et al, 1996).

### Previous Antidepressant Treatment

- Never adequate trial
- Failed adequate trial

<table>
<thead>
<tr>
<th>% Response to ECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>91%</td>
</tr>
<tr>
<td>63%</td>
</tr>
</tbody>
</table>

The remission rates with bitemporal ECT (N=216) do not significantly decrease with increasing medication resistance.

(Rasmussen, et al.2007)
Star-D Remission Rates-4
Overall remission rate (QIDS-SR16)= 67%

(Rush, et al.2006)

The remission rates with bitemporal ECT (N=216) do not significantly decrease with increasing medication resistance.

(Rasmussen, et al.2007)
Pre-ECT Workup

- History
- Physical Exam
- Electrolytes
- Creatinine
- CBC
- Liver function tests
- Urinalysis
- EKG

Consider

- Brain CT
- EEG
- Spine X-Ray
- Chest X-ray

Relative Contradictions to ECT

- Intracranial neoplasm
- Recent cerebral vascular accident
- Subdural hematoma
- Recent myocardial infarction
- Angina
- Congestive heart failure
- Acute or chronic respiratory disease
# Administration of ECT

- NPO
- Hyperoxygenation
- Short acting anesthetic – Etomidate or Methohexital
- Succinylchlorine + blood pressure cuff techniques

<table>
<thead>
<tr>
<th>Consider</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>Lithium</td>
</tr>
<tr>
<td>Atropine</td>
<td>Anticonvulsants esp. Benzodiazapines</td>
</tr>
<tr>
<td>Labetalol</td>
<td>(Consider Zolpidem for sleep)</td>
</tr>
<tr>
<td>Esmolol</td>
<td></td>
</tr>
</tbody>
</table>

## Should an Antidepressant Medication be given with ECT?

- ECT response rates significantly better with concomitant antidepressant (venlafaxine or nortriptyline) compared with placebo.
Studies Comparing Bilateral and Unilateral ECT

- Bilateral better than Unilateral 13
- Bilateral equal to Unilateral 14
- Unilateral better than Bilateral 2

Right Unilateral ECT at 6X seizure threshold is as effective as Bilateral ECT with significantly less cognitive disturbance.

<table>
<thead>
<tr>
<th>ECT</th>
<th>Remission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral</td>
<td>65%</td>
</tr>
<tr>
<td>RUL- 6X</td>
<td>60%</td>
</tr>
<tr>
<td>RUL-2.5X</td>
<td>30%</td>
</tr>
<tr>
<td>RUL-1.5X</td>
<td>35%</td>
</tr>
</tbody>
</table>

Sackeim et al, 2000
High Dose Right Unilateral ECT as Efficacious as Bitemporal ECT with Less Cognitive Disturbance

- Abrams et al, 1991 (n=38)
- Sackeim et al, 1993 (n=96)
- Sackeim et al, 2000 (n=80)

Right Unilateral ECT Efficacy Increases with Intensity

- Right Unilateral (RUL) ECT given at seizure threshold is significantly less effective than RUL ECT given at 2.25 to 12.6 times seizure threshold
- Cognitive disturbance also increases with intensity

McCall et al, 2000
Pulse and sine wave comparison. Energy = area under curve

Waveform characteristics of sine wave and square wave stimulus generators under typical operating conditions with standard patient impedances.

Brief Pulse Stimulus Parameters

Charge: (pulse width) x (twice frequency) x (duration) x (peak current) [milli coulombs]

Energy: (charge) x (peak current) x (dynamic impedance) / 1000 [Joules]
Ultrabrief Pulsewidth ECT

- Ultrabrief Pulsewidth: 0.25-0.3 msec
- More efficient induction of seizure than 1.0 msec pulsewidth
- > 1.0 msec PW falls within the refractory period of the neurons.
- Able to induce seizure with 1-10% of machine output with ultrabrief compared to 30-40% with 1.5 ms pulsewidth.
- Data from Columbia shows that right unilateral ultrabrief at 6x seizure threshold is as effective as bitemporal with less memory disturbance.

Sackeim et al., Brain Stimulation, 2008

Ultrabrief ECT Study

- 90 depressed subjects randomized to:
  - Brief Pulse (1.5 msec) - Right Unilateral 6X seizure threshold
  - Ultrabrief Pulse (.30 msec) - Right Unilateral 6X seizure threshold
  - Brief Pulse (1.5 msec) – Bitemporal 2.5 x seizure threshold.
  - Ultrabrief Pulse (.30 msec) – Bitemporal 2.5 x seizure threshold.
Remission Rates One-Week Post ECT

Sackeim et al, 2008

Amnesia for Autobiographical Memory Post-ECT

Sackeim et al, 2008
Starting with Ultrabrief RUL (.3pw) vs Starting with Bitemporal (1.0pw)

- Retrospective Chart Review
- Starting with Ultrabrief RUL, 46% switched to Bitemporal ECT. Mean # of sessions = 9.4
- Starting with Bitemporal. Mean # of sessions = 7.7.
- An Ultrabrief RUL session may be less effective than a Bitemporal session.

McCormick, 2009

**Ketamine Augmentation of ECT**

![Graph showing Montgomery Asberg Depression Rating Scale (MADRS) over time for different treatment groups.](graph)

*Notes: RUL indicates right unilateral (N = 22); RUL UB, right unilateral ultra brief (N = 78); Ketamine with RUL UB (N = 7); Placebo (N = 8).*  
Loo, 2009
The following slides show a typical two lead EEG during an ECT treatment.

Recruitment

Tonic phase of seizure

Clonic phase of seizure
Clinical Response to ECT associated with some EEG characteristics:

- Greater Post-ictal Suppression
- Greater Left-Right Coherence
- Increased delta and theta in the prefrontal regions.
- Seizure duration a weak predictor.
Adverse Effects to ECT
- Death – 1/10,000 to 1/20,000
- Post-Ictal Confusion
- Memory Disturbance
- Headache
- Muscle aches
- Mania

Memory Disturbance with ECT

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before ECT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After ECT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retrograde Amnesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anterograde Amnesia</td>
</tr>
</tbody>
</table>
Bitemporal ECT has some persistent retrograde amnesia at 2 month follow-up

- Nondepressed control group
- Greater for impersonal memories than for personal
- RUL-2.5x threshold had much less memory disturbance than bilateral

Lisanby et al, 2000

Right Unilateral ECT at 6X seizure threshold has much less cognitive disturbance than Bilateral ECT

- Anterograde Memory
- Retrograde memory
- Mini-mental state
- Paired Words

Sackeim et al, 2000
AGE-RELATED COGNITIVE EFFECTS OF ECT AND ECT-INDUCED MOOD IMPROVEMENT IN DEPRESSIVE PATIENTS

P. R. Bosboom, M.Sc., and J. B. Deijen, Ph.D.*

This exploratory study investigated the interaction between electroconvulsive therapy (ECT) treatment-effect, reduced depression, and neuropsychological outcome in relation to age. Follow-up neuropsychological assessment was conducted with depressive patients treated with ECT. From a potential sample of 45 patients, the neuropsychological measures (pre-ECT; three times post-ECT, up to 12 months) and clinical data from the remaining 21 patients who completed all assessments were evaluated (mean age = 56.76; SD = 14.12; range, 31–79). ECT resulted in a decrease in the depression scores. A distinct impact of ECT and depression decrease on cognitive domains was found. Depression alleviation was mainly associated with improvement in cognitive domains such as memory, information processing, and executive function. ECT improved cognitive domains such as information processing and perception. Short-term cognitive improvement was greater in older patients but showed an increase similar to that at long-term follow-up in younger patients (< 60). Current findings provide evidence that ECT may improve cognitive functioning in undemented elderly, which has strong clinical relevance concerning the use of ECT. Depression and Anxiety 23:93–101, 2006. © 2006 Wiley-Liss, Inc.

Cognition functions often improve with ECT

<table>
<thead>
<tr>
<th>Cognitive test variable*</th>
<th>Without covariates</th>
<th>With covariates</th>
<th>Without covariates</th>
<th>Without covariates</th>
<th>With covariates</th>
<th>Without covariates</th>
<th>With covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMS Paired Associates</td>
<td>0.23</td>
<td>0.029</td>
<td>0.23</td>
<td>0.077</td>
<td>0.47</td>
<td>0.049</td>
<td>0.48</td>
</tr>
<tr>
<td>H-Word List</td>
<td>0.23</td>
<td>0.029</td>
<td></td>
<td></td>
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<tr>
<td>BVST Correct Responses</td>
<td>0.30</td>
<td>0.046</td>
<td>0.27</td>
<td>0.011</td>
<td>0.39</td>
<td>0.039</td>
<td>0.45</td>
</tr>
<tr>
<td>WMS Visual Reproduction</td>
<td>0.27</td>
<td>0.017</td>
<td>0.28</td>
<td>0.019</td>
<td>0.25</td>
<td>0.041</td>
<td></td>
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<tr>
<td>WMS Orientation</td>
<td></td>
<td></td>
<td>0.30</td>
<td>0.013</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MOCQ Semantic Recent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>GIT Word Matrices</td>
<td>0.38</td>
<td>0.007</td>
<td>0.53</td>
<td>0.017</td>
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<td></td>
</tr>
<tr>
<td>Stroop Card I speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.48</td>
<td>0.026</td>
<td>0.48</td>
</tr>
<tr>
<td>Stroop Card II speed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.40</td>
<td>0.048</td>
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<tr>
<td>Stroop Card III words</td>
<td>0.24</td>
<td>0.037</td>
<td>0.26</td>
<td>0.043</td>
<td>0.41</td>
<td>0.028</td>
<td>0.47</td>
</tr>
<tr>
<td>WMS Digit Symbol</td>
<td>0.28</td>
<td>0.017</td>
<td>0.28</td>
<td>0.024</td>
<td>0.41</td>
<td>0.028</td>
<td>0.47</td>
</tr>
<tr>
<td>WMS Mental Control</td>
<td>0.22</td>
<td>0.043</td>
<td></td>
<td></td>
<td>0.65</td>
<td>0.005</td>
<td>0.56</td>
</tr>
<tr>
<td>GIT Incomplete Pictures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.65</td>
<td>0.005</td>
<td>0.56</td>
</tr>
<tr>
<td>GIT Visualization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.65</td>
<td>0.005</td>
<td>0.56</td>
</tr>
</tbody>
</table>

*See text for description of tests.

1Session 1, one week before ECT index; session 2, one week after ECT index; session 3, 6 months after session 1; 6 months after session 3.

Depression and Anxiety DOI 10.1002/an

Bosboom, 2006
Session 1, one week before ECT index;
Session 2, one week after ECT index;
Session 3, 6 months after session 2;
Session 4, 12 months after session 2.

Bosboom, 2006

Patients given more than 100 Lifetime ECT vs. Matched Non-ECT Patients

No differences in cognition scores:

- Mini-Mental Status
- Buschke Selective Reminding Test
- Subjective Memory Questionnaire:
  Events long ago, Events a few minutes ago, Names and faces of people, Events a month from now, Global.

Case Reports of Memory Not Returning to Normal; May Be Due to Any of Several Factors

- A sensitization to normal forgetting following the transient organic amnesia that often accompanies the ECT treatment course
- Residual and/or recurrent symptoms related to the condition for which ECT was used.
- Concurrent medication use or substance abuse.
- Comorbid Brain Disease
- A Conversion type of syndrome
- Psychological reinforcemnt of transient organic losses (secondary gain)
- An idiosyncratic neurobiological effect.  

Mankad, 2010

Does ECT Alter Brain Structure?

Animal Studies

- Qualitative analyses using perfusion fixation
- Neuronal counting
- Electrical amperage – 1,800 mA
- Thermal effects
- Blood brain barrier changes
- Protein synthesis
- DNA single strand break
Does ECT Alter Brain Structure?

Human Studies

- Computerized axial tomography
- Magnetic resonance imaging
- Paired Words
- Autopsies of ECT patients
- Autopsies of epilepsy patients

“There is No Credible Evidence That ECT Causes Structural Brain Damage”

Devanand et al,
Amer J of Psychiatry 1994, 151:957-970
Proposed Mechanisms of Action ECT

- Introjected anger
- Memory disturbance
- Increased NE, serotonin, Brain-Derived Neurotrophic Factor (BDNF), GABA release
- Down regulation of beta-adrenergic receptors
- Endogenous anticonvulsant Production
- Resynchronizes the “Body Clocks” (Circadian, Ultradian such as 90 minute REM-NREM cycle, or EEG coherence)
  - Analogous to cardiac shock

Good ECT Response Associated with:

- Post-ictal suppression of EEG.
- Left-Right Coherence (synchrony) of EEG during the ECT
- Increased delta and theta in the prefrontal regions in post-ictal period.
ECT Seizure Threshold

- Males higher than females.
- Depressed higher than manic.
- Increases with age.
- Increases as the Number of ECT Treatment Increases
- Increases are Related to the Degree of Response to ECT
- Greater Increases with Bilateral than Unilateral ECT
GABA Hypothesis of Depression

- GABA decreases with stress
- GABA decreased in CSF of Depressed Patients - 7 studies
- GABA decreased in plasma of depressed patients
- GABA decreased in magnetic resonance spectroscopy in Depressed patients
- GABA increases functional connectivity in EEG
- ECT increases GABA levels in depressed patients.
- ECT increases GABA-A receptors in depressed patients.

Brain-Derived Neurotrophic Factor (BDNF) Increases with:

- Antidepressant medication (Duman, 1997)
- Electroconvulsive therapy (Duman, 2000)
- Transcranial Magnetic Stimulation (Muller, 2000)
ECT Increases Neurogenesis in Rats

- Compared to sham stimulation, a single ECT increases the number of newborn neuronal cells in the dentate gyrus of the rat (bromodeoxyuridine)
- Sustained survival of cells for at least 3 months
- Increased synaptogenisis (neuronal cells adhesion molecule) following ECT.
- No increase in apoptotic cells even after 10 ECTs

Maben et al, 2000, Jorgenson and Bolwig, 1979

Functional Network Connectivity Changes with ECT Response

- Older MDD subjects (N=12) had fMRI before and after ECT.
- Analysis focused on four networks affected in MDD: the subcallosal cingulate gyrus, default mode, dorsal lateral prefrontal cortex, and dorsal medial prefrontal cortex (DMPFC)
- Remission associated with the ECT reverses the relationship from negative to positive between the posterior default mode (p_DM) and two other networks: the DMPFC and left dorsal lateral prefrontal cortex (l_DLPFC).
- Relative to demographically healthy subjects (n = 12), the FNC between the p_DM areas and the DMPFC normalizes with ECT response.
- The differences between ECT remitters and non-remitters suggest that this increased FNC between p_DM areas and the left dorsolateral prefrontal cortex is a neural correlate and potential biomarker of recovery from a depressed episode.

(Abbott, 2013)
Effects of ECT on Brain Functional Activation and Connectivity in Depression

• fMRI during working memory and affective tasks and during rest in 6 depressed patients before and after ECT.
• Activation during both tasks was generally found to be decreased after ECT.
• Remission of depression was significantly associated with reduced affective deactivation after ECT in the orbitofrontal cortex (P = 0.03).
• Whole-brain functional connectivity of the anterior cingulate cortex showed a consistent increase in connectivity to the right dorso-lateral prefrontal cortex and posterior cingulate cortex after ECT.
ECT reduces frontal cortical connectivity in depression.

- fMRI before and after ECT in 9 depressed patients.
- In the left dorsolateral prefrontal cortical region (Brodmann areas 44, 45, and 46), where the average global functional connectivity was considerably decreased after ECT treatment ($P < 0.05$).
- The decrease in functional connectivity was accompanied by a significant improvement ($P < 0.001$) in depressive symptoms.
- “hyperconnectivity hypothesis” in depression

Perrin, 2012

Main Points

- Medication-Resistance Depression is common and usually has poor response rates to further antidepressant trials; ECT is usually effective in this population.
- Ultra-Brief Right Unilateral ECT is very effective and has minimal memory disturbance.
- ECT increases neuroplasticity and changes the connectivity in the brain.
Transcranial Magnetic Stimulation (TMS)

- An electromagnetic applied to the scalp creates a changing magnetic field which induces a small localized electric current in the cortex.
- Magnetic fields meet little resistance from skin, bone, CSF, etc. compared to electrical current. Usually not painful.
Time-varying electrical current in a coil produces focal 2 tesla magnetic field that passes unimpeded through skull and induces current in neurons and behavioral change.

Repetitive Transcranial Magnetic Stimulation (rTMS) vs TMS

- Using multiple capacitors, rTMS machines are able to deliver regular repeated pulses to a single scalp site.
- rTMS may have sustained effects.
rTMS Parameters

- Intensity (% of the Threshold for the Abductor Pollicis Brevis)
- Frequency
- Duration of Trains
- Intertrain Interval
- Number of Trains Per Session
- Number of Sessions

10 and 20 Hz rTMS Trains of 100 Microsecond Pulses

- 10 Hz x 5 Seconds, 32 Trains per session, 15 sessions
- 5 SECONDS

- 20 Hz x 2 Seconds, 20 Trains per session, 10 sessions
- 2 SECONDS
The Frequency of rTMS May Be Important

- High Frequency
  >1 Hz
  Rapid Rate
  • May Facilitate (like Long-Term Potentiation?)

- Low Frequency
  ≤ 1 Hz
  Slow Rate
  • May Inhibit (like Long-Term Depression?)

ECT and rTMS

<table>
<thead>
<tr>
<th></th>
<th>ECT</th>
<th>rTMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charge Density</td>
<td>20</td>
<td>1-2</td>
</tr>
<tr>
<td>(microcoulombs/cm2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulus</td>
<td>Diffuse</td>
<td>Focal</td>
</tr>
<tr>
<td>Memory Disturbance</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Post-Ictal Confusion</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Now that we are learning more about the neuroanatomy of psychiatric illness through functional neuroimaging, the **FOCAL** nature of TMS becomes very important. For example,

- Low prefrontal cortex activity in depression
- Increased activity in the temporal-parietal area in auditory hallucinations.

### Effects of ECT and rTMS in Animals

<table>
<thead>
<tr>
<th></th>
<th>ECT</th>
<th>rTMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-Adrenergic</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Receptors Down-regulated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apomorphine Stereotopy</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porsolt Swim Test</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Increases Seizure Threshold</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Possible mechanisms of action

- Brain activity changes with acute stimulation
- Resynchronization effects
- Changes in cortical excitability with repeated stimulation
- Anticonvulsive activity
- Changes in cortical plasticity
- Neurotransmitter modulation
- Neuroendocrine changes

Acute effects of TMS

- Most likely causes depolarization of cortical interneurons

- Indirect effects on main cortical output neurons (pyramidal cells)

- Acute effects may be distributed throughout brain
Approximate Depth Limit of Direct Stimulation With Current TMS Coils

TMS has **indirect** effects.

- TMS to Dorsolateral Prefrontal Cortes affects Medial Prefrontal Cortex, Anterior Cingulate, Insula, Thalamus, and Hypothalamus (TSH levels increase acutely with TMS.)
- With TMS to the motor cortex, both the ipsilateral and contralateral motor cortex shows increases in fMRI activity.
Response (50% or more decrease in HAMD) and Remission (HAMD <8) in TMS and Sham Groups

P=.008
P=.033

Avery et al, 2006

The Treatment-Placebo Differences in Response Rates are More Meaningful than Absolute Response Rates.

- Antidepressant-placebo differences=10-20%
- Fluoxetine-placebo difference= 14%
- Venlafaxine-placebo difference=20%
- Current study: TMS-sham difference=25%

TMS result is clinically significant
TMS evidence base in 2010

There have now been >30 RCTs of TMS, with positive metaanalyses of this literature1-3

FDA approval for TMS in MDD in 2008 based on results of industry-sponsored, large sample (n=301) RCT4

Now have an independent replication in an NIH sponsored (n=199) RCT5

Database available at: http://www.brainstimjml.com/content/mmc_library
89 randomized controlled studies, 52 open label studies


Meta-analysis efficacy in Treatment Resistant Depression (2008)

Figure 1 Metaanalysis results for clinical response showing risk difference between active and sham rTMS in all studies

n=24 RCTs, with 1092 patients

(n=9 RCTs: >1 ADM failure)
(n=15 RCTs: >2 failures)

Lam RW et al. Can J Psy 2008

Effect Size d=0.48 (CI: 0.28-0.69)
NNT (response)=6; NNT (remission)=7
Slow Frequency TMS metaanalysis (2010)

(9 RCTs, 252 patients, 1 Hz to right PFC)

<table>
<thead>
<tr>
<th>Active TMS</th>
<th>Sham TMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=134</td>
<td>n=118</td>
</tr>
</tbody>
</table>

Effect Size = 0.63 (CI:0.03 – 1.24)

Schutter DJ LG Psychol Med 2010

Neuronetics TMS Studies
N=301

- **Study No. 44-01101**
  - Demonstration of acute efficacy vs Sham
  - Safety
  - 6 weeks acute/3 weeks taper

- **Study No. 44-01102**
  - Demonstration of acute efficacy in non-responders (active or sham)- Open
  - Safety
  - 6 weeks acute/3 weeks taper

- **Study No. 44-01103**
  - Characterize long-term maintenance of effect in rTMS responders
  - 6 months

O’Reardon et al, Biological Psychiatry, 2007
Cumulative sustained response (HAMD17) for all subjects allocated to active TMS in Study 101 through acute treatment phases of Studies 101 and 102. 
[Sustained response definition: first visit of ≥ 50% reduction from baseline score and ≥ 25% reduction maintained at all later time points]
Duration of TMS Response

- Responders to TMS in acute phase, N=99
- 6-month follow-up of with addition of antidepressant and reintroduction of TMS if worsening.
- Symptom worsening requiring TMS =38%
- 84% (32/38) reached symptom benefits from TMS.

- **Relapse Rate = 13%**
  (vs 40% relapse rate in STAR-D remitters – one previous antidepressant failure)
  (vs a mean of 23% relapse rate in antidepressant continuation studies.)
  (vs ECT + pharmacotherapy, 32% relapse rate; or ECT continuation ECT, 37%)

Janicak et al, 2010
TMS is less effective than ECT, particularly in treating psychotic depression

Berlim et al, 2013

Transcranial Direct Current Stimulation

Exp Neurol. 2009 Sep;219(1)
Transcranial Direct Current Stimulation (tDCS) in Major Depression

Boggio, 2008
Nitsche, 2009

Transcranial Pulsed Electromagnetic Field (PEMF) Treatment:
Maximum 1.9 Gauss (1.9 milliTesla) at .5 cm
### ECT vs TMS vs PEMF: Physics

<table>
<thead>
<tr>
<th></th>
<th>ECT</th>
<th>TMS</th>
<th>PEMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity of Stimulation</td>
<td>High</td>
<td>Lower</td>
<td>Very Low</td>
</tr>
<tr>
<td>E-Field</td>
<td>~3000 mV/cm</td>
<td>~1000 mV/cm</td>
<td>~2 mV/cm</td>
</tr>
<tr>
<td>Hz</td>
<td>50-60</td>
<td>1-50 (usually 1-10)</td>
<td>55</td>
</tr>
<tr>
<td>Action Potentials?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Diffuse or Focal</td>
<td>Diffuse</td>
<td>Focal + Indirect effects</td>
<td>Diffuse</td>
</tr>
</tbody>
</table>

**The pulse – and its shape**

- **B dB/dt**
- **EMF = dB/dt**
- **Current in coil**
- **E-field measured in a coil**
- **55 Hz**
## ECT vs TMS vs PEMF: Clinical Administration

<table>
<thead>
<tr>
<th></th>
<th>ECT</th>
<th>TMS</th>
<th>PEMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized Seizure?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Muscle Relaxant?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Anesthesia?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Anesthesiologist?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

## ECT vs TMS vs PEMF: Side Effects and Clinical Administration

<table>
<thead>
<tr>
<th></th>
<th>ECT</th>
<th>TMS</th>
<th>PEMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion for metal in body?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Seizure Risk?</td>
<td>Seizure Intended</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Memory Disturbance?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Self-Administered?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Administered in home?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cost</td>
<td>Cost ++++</td>
<td>Cost +++</td>
<td>Cost +</td>
</tr>
</tbody>
</table>
PEMF Safety

- No Seizure Risk: 35 mV required for an action potential.
- Magnitude and frequency of PEMF similar to naturally occurring electrical activity created by action potentials of the brain.
- PEMF at 55 Hz is an Extremely Low Electromagnetic Field (ELF-EMF)
- Much lower than cell phone frequency: 800 Megahertz
- “The scientific evidence suggesting that ELF-EMF exposures pose any health risk is weak.” NIH and National Institute of Environmental Health Sciences (NIEHS).
- No ionizing radiation from PEMF
- Much lower intensity than MRI: MRIs not found to cause mutations or changes in DNA.

Transcranial Pulsed Electromagnetic Field (T-PEMF) Therapy (in 50 Medication-Resistant Depressed Patients)

- Effect Size = 0.62
- p<.01

Martiny et al, Biol. Psych, 2010
ECT vs TMS vs PEMF: Efficacy in Depression

<table>
<thead>
<tr>
<th></th>
<th>ECT</th>
<th>TMS</th>
<th>PEMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant Effect Size (d)</td>
<td>0.91</td>
<td>0.39, 0.48, 0.55</td>
<td>.62</td>
</tr>
</tbody>
</table>

Response Rates in PEMF Study and Mean Response Rates in the TMS Meta-analysis (N=1107)

Martiny et al, 2010  
Ebmeier and Hermann, 2008
**Remission Rates in PEMF Study** and Mean Remission Rates in the US TMS Multisite Studies (N=500)

Martiny et al, 2010

George et al, 2010; O’Reardon, 2007

---

**Rationale for Investigating VNS in Depression**

- Long-standing use of VNS to access limbic structures for research
- Known neuroanatomic vagus projections
- PET scans and animal c-fos data showing VNS effects in mood-regulating regions
- Mood effects in VNS patients with epilepsy
- Use of anticonvulsants as mood stabilizers
- Neurochemical and monoamine data on VNS
Vagus Nerve Stimulation

VNS: Afferent Pathway to the Brain

- Hypothalamus
- Thalamus
- Parabrachial Nucleus
- Locus Coeruleus
- Amygdala
- Hippocampus
- Pons
- Medulla
- Medial Reticular Formation
- Spinal Cord
- Area Postrema
- Nucleus of the Solitary Tract
- Solitary Tract
- Nucleus of the Solitary Tract
- Nodose Ganglion
- DMN
- Cuneatus
- Nucleus Cuneatus
- Insula, Anterior Cingulate Gyrus, Orbitofrontal Cortex
Vagus Nerve Stimulation (VNS)

- Mild electrical pulses applied to the left vagus nerve in the neck for transmission to the brain
- Intermittent stimulation
  - 30 sec on/5 min off
  - 24/7 for 10 years
- Magnetic empowerment
  - On-demand stimulation
  - Acute side effects control
- Simple in-office programming (dosing) by treating physician
- 100% patient adherence

VNS Pulse Generator & Lead

- Implanted in over 22,000 patients worldwide
- Pacemaker-like pulse generator
- Model 102 for use with a single-pin lead
- 6.9 mm thick (33% thinner than Model 101)
- Weighs 25 g (34% lighter than Model 101)
- 6- to 11-year battery life
VNS Therapy for Chronic or Recurrent Treatment-Resistant Depression

D-02 Study

D-02 Study: Methods

- Based on D-01 pilot study experience
- Similar in design to D-01
- Randomized, blinded, placebo-controlled
- Blinded assessments of clinical outcomes (eg, HRSD$_{24}$)
- Certification and ongoing qualification of clinical ratings
- Includes monthly/quarterly long-term follow-up
- Extreme levels of treatment resistance are excluded
D-02 Study Design

10 weeks of VNS (8 weeks fixed dose stimulation)

D-02 Acute Response Rates
(n=222 – Evaluable Group)

\[ P = 0.238 \quad P = 0.032 \]
D-02 Treatment-Emergent AEs (≥5%) Possibly Related to Implantation

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Total (N=235)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of subjects with at least one adverse event</td>
<td>38</td>
</tr>
<tr>
<td>Device site pain</td>
<td>23</td>
</tr>
<tr>
<td>Device site reaction</td>
<td>14</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
</tr>
<tr>
<td>Incision</td>
<td>36</td>
</tr>
<tr>
<td>Neck pain</td>
<td>7</td>
</tr>
<tr>
<td>Pain</td>
<td>7</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>11</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
</tr>
<tr>
<td>Hyposthesia</td>
<td>11</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6</td>
</tr>
<tr>
<td>Cough increased</td>
<td>6</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>13</td>
</tr>
<tr>
<td>Voice alteration</td>
<td>33</td>
</tr>
<tr>
<td>Incision site reaction</td>
<td>29</td>
</tr>
</tbody>
</table>

Vocal cord paralysis 1.2%; asystole <1%; bradycardia <1%.

D-02 Long-Term Patient Outcomes

IDS-SR and HRSD\textsubscript{24} Response and Remission (Evaluable Patients)

- 3 months
- 6 months
- 9 months
- 12 months

![Graph showing percentage of response and remission over time for IDS-SR and HRSD\textsubscript{24} for different time points.]
D-04: An Observational Study of Long-Term Outcomes in Treatment-Resistant Depression
• 13 total study sites including 12 from D-02
• Similar study enrollment criteria to D-02
• Similar age and sex distribution to D-02
• Similar level of treatment resistance to D-02
• Similar dates of enrollment to D-02
• Comparable clinical and quality of life assessments to D-02
• Represents a control/reference group

D-02 vs D-04: 12-Month HRSD$_{24}$ Response and Remission Rates

12-Month HRSD$_{24}$ Response and Remission Rates
(Evaluable Patient Population; Observed Data)

<table>
<thead>
<tr>
<th></th>
<th>D-02 (n=205)</th>
<th>P = .005</th>
<th>D-04 (n=124)</th>
<th>P = .08</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>30%</td>
<td>13%</td>
<td>17%</td>
<td>7%</td>
</tr>
<tr>
<td>Remission</td>
<td>30%</td>
<td>17%</td>
<td>30%</td>
<td>25%</td>
</tr>
</tbody>
</table>

\[ P = .005 \]
\[ P = .08 \]
Deep Brain Stimulation

Deep Brain Stimulation Study

- Treatment Resistant Depression - at least 4 failed treatments
- Mean duration of current episode – 7 years
- Open study
- N=20
- DBS to the Subcallosal Cingulate Gyrus
- Lozano, Mayberg et al, 2008
Figure 1. Mean HRSD-17 score for 20 patients with TRD receiving SGC DBS at baseline and at subsequent visits over a 12-month period. The values at all time points from 1 to 12 months are significantly different compared with baseline $p < .001$. Error bars indicate standard deviation. DBS, deep brain stimulation; HRSD-17, 17-item Hamilton Rating Scale for Depression; SGC, subcallosal cingulate gyrus; TRD, treatment-resistant depression.

Figure 2. Patients meeting response or remission criteria after DBS. The proportion of patients responding or reaching remission increased over time to plateau from 6 to 12 months. DBS, deep brain stimulation.
Increased Blood Flow in the Subgenual Anterior Cingulate (Cg25) In Major Depression—Changes with Deep Brain Stimulation

Mayberg, 2005
Critical Change Necessary for Response: ↓ Subcallosal Cingulate Activity (SCC25)

Increased SCC25 activity seen with induced depressed mood

Decreased SCC25 activity seen with diverse successful treatments

(Other changes seen, but more treatment specific)

Putative Mood Regulation Model: Regions and Pathways Involved in Depression and Treatment Response

attention-cognition-context

CORTEX

Placebo

SUBCTX

Drug

LIMBIC

Mayberg, Br Med Bull, 2003
Introduction

According to a national U.S. survey conducted between 2001 and 2003, 16.6% of adults will experience a major depressive disorder (MDD) in their lifetime. Failure to respond to initial treatment plans involving psychotherapy and/or an antidepressant medication is common. Treatment-resistant depression, or TRD, is a term used to describe MDD that does not respond to initial treatment with antidepressant medication, which is considered appropriate for moderate to severe MDD. A large multicenter study (STAR*D) found that approximately one third of MDD patients achieved remission with an initial antidepressant and approximately half achieved remission after a second antidepressant trial, provided the patients remained in treatment. Although a standard definition of TRD is not recognized, a recent evidence report prepared for the Agency for Healthcare Research and Quality (AHRQ) concluded that there is an emerging consensus that failure of ≥ 2 prior adequate pharmacologic trials is an appropriate definition. Treatment resistance may also occur in depression related to bipolar disorder.

Nonpharmacologic treatments are often tried when pharmacotherapy has failed or has proved intolerable to a patient. Such options include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), transcranial direct current stimulation (tDCS), and vagus nerve stimulation (VNS).

The Centers for Medicaid & Medicare Services has no national policy on ECT, TMS, DBS, or tDCS. The FDA has approved ECT for depression and has approved TMS and VNS specifically for TRD. The FDA has not approved DBS or tDCS for depression.

Policy Context

Nonpharmacologic treatments for depression that does not respond to first line treatments was selected for review based on concerns about the safety, efficacy and cost of the treatments. Depression is relatively common among adults and contributes to or is associated with higher rates of other disease processes, disability and reduced quality of life. This review will help to identify safe and effective evidenced-based care for TRD.

Scope of this HTA

VNS will not be covered in this report. Washington HTA previously reviewed VNS in 2009 (Vagus Nerve Stimulation for Depression and Epilepsy). An updated search for new literature conducted in August 2013 revealed no new evidence likely to change the conclusions of the 2009 report.

Population: Adults with major depressive disorder or bipolar depression who have not responded to prior adequate pharmacologic treatments.
Interventions: Nonpharmacologic treatments for depression, including electroconvulsive therapy (ECT), deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS).

Comparators: Sham treatment, treatment as usual, other nonpharmacologic treatment (including psychotherapy as a new treatment in response to treatment failure), pharmacologic treatment (a new medication to be tried in response to treatment failure), or combination therapy that does not include the nonpharmacologic therapy of interest.

Outcomes: Response, remission, depression severity, functional status, quality of life (QOL)

DRAFT Key Questions
1. a. What is the evidence of a reliable and valid case definition for treatment-resistant depression (TRD)?
   b. Is there a reliable and valid definition of clinically meaningful improvement for depression and function for patients treated for TRD?

2. a. Are the following nonpharmacologic treatments effective for TRD?
   - Electroconvulsive therapy (ECT)
   - Repetitive transcranial magnetic stimulation (rTMS)
   - Deep brain stimulation (DBS)
   - Transcranial direct current stimulation (tDCS)
   b. Does the effectiveness of these treatments vary according to treatment intensity, duration of treatment, use in an augmentation versus switch strategy, or any other variation in the manner in which TRD treatment was administered?

3. What adverse events, including withdrawal from treatment, are associated with nonpharmacologic treatments for TRD?

4. Does the effectiveness of nonpharmacologic treatments for TRD vary by subpopulation defined by such factors as: age, race/ethnicity, gender, disease severity, disease duration, depression diagnosis (unipolar or bipolar depression), symptom type (e.g., psychotic, postpartum), comorbidities, or number and type of prior treatments (including other nonpharmacologic treatments)?

5. What are the cost implications and cost-effectiveness of nonpharmacologic therapies for TRD?

Public Comment & Response
Submit comments to the HTA program at shtap@hca.wa.gov.
For additional information on key questions and public comment.