Washington State Health Care Authority

Health Technology Assessment

Nonpharmacologic Treatments for Treatment-Resistant Depression

Draft Key Questions: Public Comments and Response

November 8, 2013

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Nonpharmacologic Treatments for Treatment-Resistant Depression

Response to Topic and Public Comments on Key Questions

November 8, 2013

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Response to Public Comments, Topic and Key Questions

Nonpharmacologic Treatments for Treatment-Resistant Depression

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

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

Comment and Source	Response
Comments on Topic	
None received.	
Comments on Draft Key Questions	
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 medication20 and that ECT lowers the mortality rate in depression compared to patients with depression not treated with ECT15. 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%.[1]"	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.

Comment and Source	Response
Key Question 1b "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."	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.
Key Question 2a The commenter summarized findings from several reviews and clinical trials with respect to the interventions of interest.	Thank you for these comments and citations. The references will be considered for inclusion in the report.
Key Question 2b "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.[14] 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	Thank you for this helpful background information. No change to Key Question.

Comment and Source	Response
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 research 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."	Thank you for this background. The reference will be considered for inclusion in the report. No change in the Key Question.
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.

Comment and Source	Response
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."	
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."	Thank you for this background. The references will be considered for inclusion in the report. No change in the Key Question.
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.

Comment and Source	Response
Key Question 1b "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."	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.
Key Question 3 "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."	Thank you for this thoughtful response.

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

(ECT).http://www.fda.gov.offcampus.lib.washington.edu/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/UCM240933.pdf (Accessed on May 25, 2011).) Up-To-Date is also a good source on information about this and other topics. The remission rates with ECT do not significantly decrease with increasing medication resistance according to one study. [5] 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%.[6] 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.[7] In this clinical setting, rTMS has been found to be associated with significant response and remission rates[8] and improves the quality of life. [9] New research in TMS may lead to even better efficacy.[10]

- 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.[11] 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.[12,13] 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.[14] 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 research 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 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.

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 subpopulations[16]. 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]

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.

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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,

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1. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *The American journal of psychiatry.* Nov 2006;163(11):1905-1917.
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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

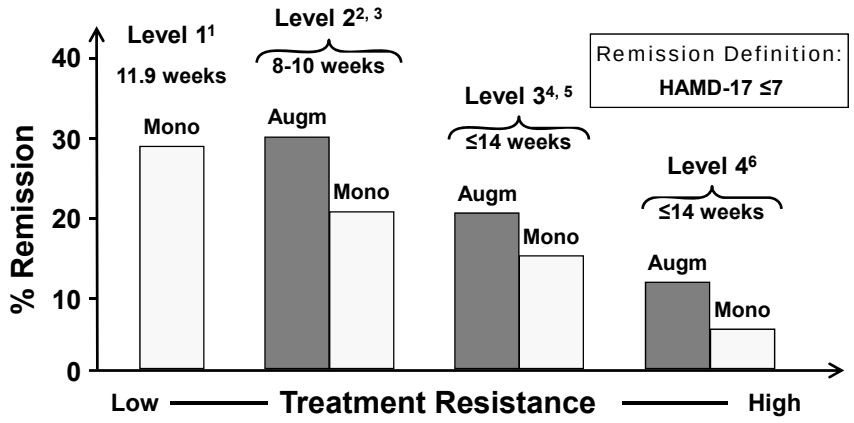
Outline

- 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



Mono = single medication regimen; Augm = combination medication treatment; [1]Trivedi MH et al. (2006), Am J Psychiatry 163:28-40; [2]Trivedi MH et al. (2006), N Engl J Med 354:1243-1252; [3]Rush AJ et al. (2006), N Engl J Med 354:1231-1242; [4]Nierenberg AA et al. (2006), Am J Psychiatry 163:1519-1530; [5]Fava M et al. (2006), Am J Psychiatry 163:1161-1172; [6]McGrath 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)

Trial	Number of participants	Standardised effect size (95% CI)
Wilson 1963[10]	12	−1·078 (−2·289 to 0·133)
West 1981[11]	25	−1·255 (−2·170 to −0·341)
Lambourn 1978[15]	40	−0·170 (−0·940 to 0·600)
Freeman 1978[12]	40	−0·629 (−1·264 to 0·006)
Gregory 1985[13]	69	−1·418 (−2·012 to −0·824)
Johnstone 1980[14]	70	−0·739 (−1·253 to −0·224)
Pooled fixed effects		−0·911 (−1·180 to −0·645)
Pooled random effects		−0·908 (−1·270 to −0·537)

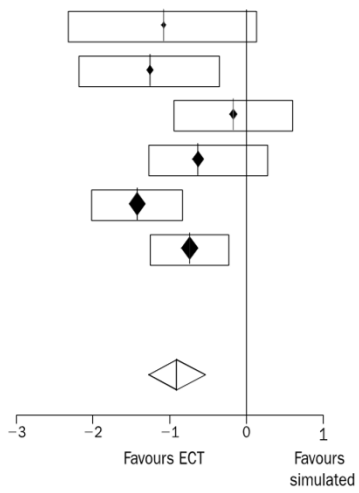


Figure 1: **Effect of ECT versus simulated ECT on depressive symptoms**

ECT vs Pharmacotherapy (UK Review Group, 2003)

Trial*	Number of participants	Standardised effect size (95% CI)
Steiner 1978[16]	12	0·369 (–0·840 to 1·578)
Wilson 1963[10]	12	–0·513 (–1·663 to 0·637)
Davidson 1978[17]	19	–1·389 (–2·449 to –0·328)
McDonald 1966[18]	22	–0·930 (–1·813 to –0·047)
Gangadhar 1982[19]	32	1·287 (0·406 to 2·169)
MacSweeney 1975[20]	27	–0·714 (–1·492 to 0·065)
Dinan 1989[21]	30	–0·196 (–0·926 to 0·534)
Janakiramaiah 2000[22]	30	–1·095 (–1·863 to –0·328)
Folkerts 1997[23]	40	–1·336 (–2·032 to –0·640)
Herrington 1974[24]	43	–1·497 (–2·174 to –0·821)
Stanley 1962[25]	47	–1·342 (–2·047 to –0·638)
Medical Research Council 1965[26]	204	–0·559 (–0·883 to –0·234)
Greenblatt 1964[27]	242	–1·683 (–2·020 to –1·346)
Pooled fixed effects		–1·010 (–1·170 to –0·856)
Pooled random effects		–0·802 (–1·290 to –0·289)

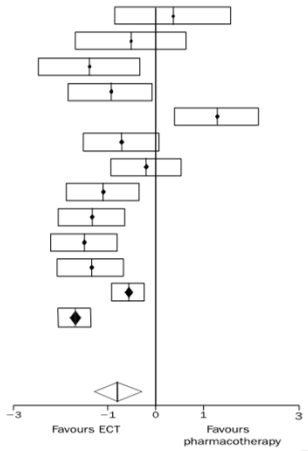


Figure 3: **Effect of ECT versus pharmacotherapy on depressive symptoms**
*Other trials not included: Kendrick 1965,[28] Bruce 1960,[29] Bagadia 1981,[30] Hutchinson 1963,[31] Robin 1962.[32]

Bitemporal vs Unilateral ECT (UK Review Group, 2003)

Trial*	Number of participants	Standardised effect size (95% CI)
Abrams 1969[33]	21	0·017 (–0·840 to 0·873)
Valentine 1968[34]	24	0·076 (–0·724 to 0·877)
Fraser 1980[35]	33	–0·320 (–1·057 to 0·416)
Abrams 1974[36]	30	0·082 (–0·678 to 0·841)
Costello 1970[37]	30	–0·342 (–1·106 to 0·422)
Fleminger 1970[38]	36	–0·317 (–1·013 to 0·380)
Taylor 1985[39]	37	–0·951 (–1·642 to –0·260)
Abrams 1991[40]	38	–0·544 (–1·192 to 0·105)
Gregory 1985[13]	46	0·215 (–0·407 to 0·837)
Levy 1968[41]	40	–0·200 (0·821 to 0·422)
Martin 1965[42]	40	0·111 (–0·510 to 0·731)
Carney 1976[43]	45	–0·188 (–0·781 to 0·404)
Horne 1985[44]	48	–0·183 (–0·750 to 0·384)
Abrams 1983[45]	70	–0·565 (–1·125 to –0·004)
Halliday 1968[46]	52	–0·171 (–0·743 to 0·401)
Sackeim 1987[48]	52	–0·818 (–1·385 to –0·252)
Malitz 1986[47]	52	–0·835 (–1·402 to –0·268)
Letemendia 1993[49]	83	–0·383 (–0·951 to 0·185)
D'Elia 1970[50]	59	–0·068 (–0·579 to 0·442)
Sackeim 2000[51]	84	–0·830 (–1·352 to –0·308)
Sackeim 1993[52]	100	–0·694 (–1·106 to –0·281)
Stromgren 1973[53]	117	–0·086 (–0·479 to 0·306)
Pooled fixed effects		–0·323 (–0·446 to –0·199)
Pooled random effects		–0·322 (–0·458 to –0·186)

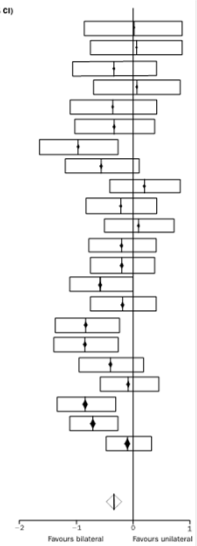


Figure 5: **Effect of bilateral versus unilateral electrode placement on depressive symptoms**
*Other trials not included: Welch 1982,[54] Papalkostas 1994,[55] Krystal 1992,[56] Daniel 1984,[57] Heshe 1978,[58] Bidder 1970.[59]

1X per week ECT vs 3X per week
2X per week ECT vs 3X per week
(UK Review Group, 2003)

Trial	Number of participants	Standardised effect size (95% CI)
Once a week *vs* three times a week		
Kellner 1992[65]	11	0·504 (−0·526 to 1·534)
Janakiramaiah 1998[66]	40	0·940 (0·287 to 1·593)
Pooled fixed effects		0·841 (0·311 to 1·370)
Pooled random effects		0·832 (−0·389 to 1·890)
Twice a week *vs* three times a week		
Gangadhar 1993[67]	30	−0·293 (−1·013 to 0·426)
Shapira 1998[68]	31	0·123 (−0·585 to 0·831)
Vieweg 1998[70]	46	−0·888 (−1·530 to −0·246)
Lerer 1995[69]	52	0·049 (−0·523 to 0·621)
Pooled fixed effects		−0·308 (−0·629 to 0·014)
Pooled random effects		−0·299 (−0·759 to 0·199)

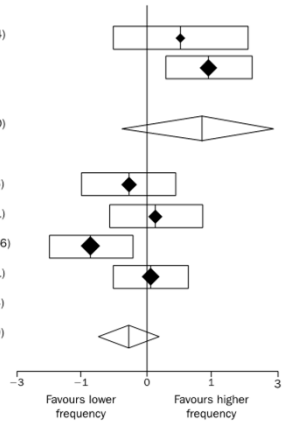


Figure 6: **Effect of frequency of ECT on depressive symptoms**

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

Trial*	Number of participants	Standardised effect size (95% CI)
McCall 1995[71]	22	0·829 (–0·042 to 1·700)
Warren 1998[73]	23	1·218 (0·463 to 1·974)
Janakiramaiah 1984[66]	40	0·273 (–0·349 to 0·896)
McCall 2000[72]	72	0·389 (–0·078 to 0·855)
Sackeim 2000[51]	80	0·368 (–0·141 to 0·877)
Sackeim 1993[52]	100	0·650 (0·239 to 1·061)
Pooled fixed effects		0·571 (0·352 to 0·790)
Pooled random effects		0·575 (0·329 to 0·829)

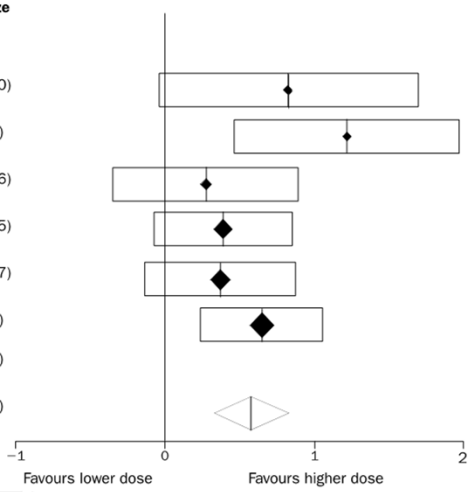


Figure 7: **Effect of higher versus lower dose of ECT on depressive symptoms**
*Other trials not included: Krystal 1996.[74]

ECT is equally effective
in treating unipolar depression and bipolar depression.

Dierckx et al, 2012

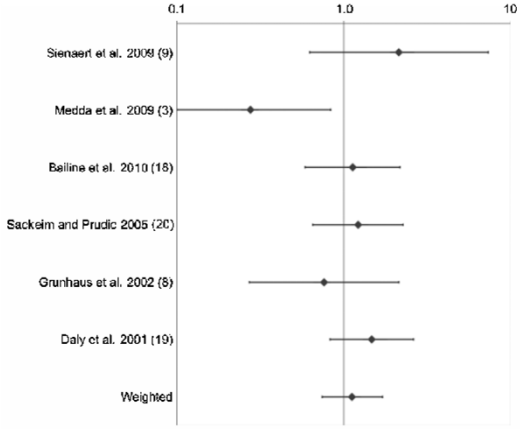


Fig. 1. Plot of the odds ratios of response to electroconvulsive therapy in patients with unipolar versus bipolar depression per study, with 95% confidence interval, after natural logarithmic transformation.

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.

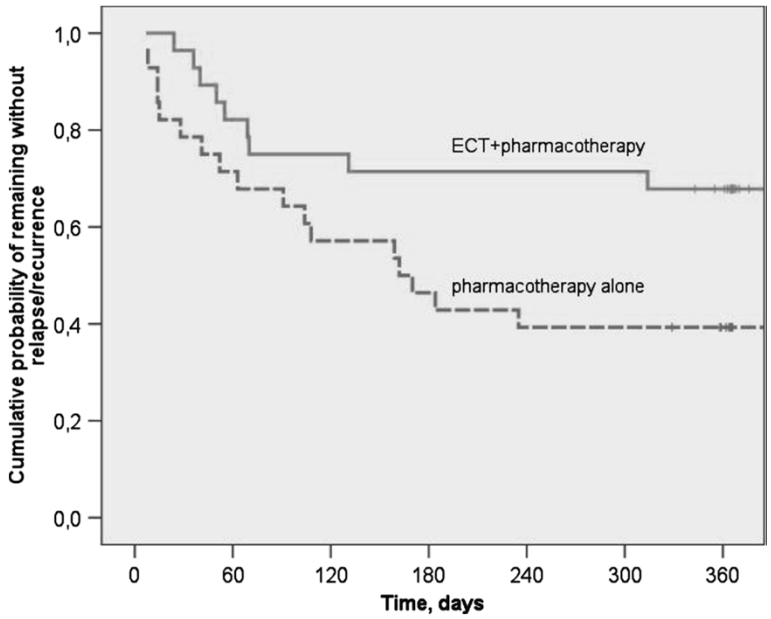


FIGURE 2. Kaplan-Meier function of the cumulative probability of remaining without relapse for patients treated with continuation ECT plus pharmacotherapy versus pharmacotherapy-alone in the intention-to-treat sample.

Nordenskjold, 2013

Continuation ECT vs Continuation Pharmacotherapy

Kellner 2006

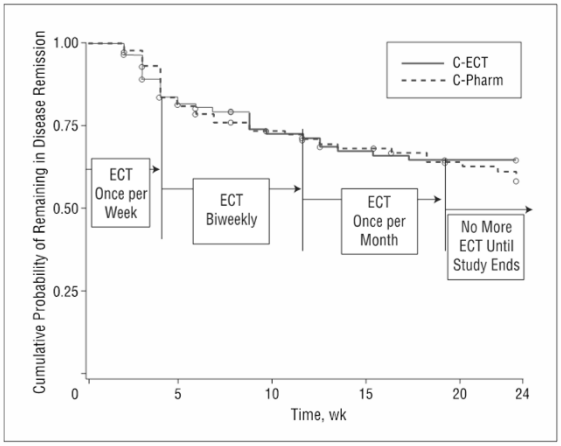


Figure 2. Kaplan-Meier curves showing proportion of patients who remained in disease remission (not disease relapse) during the continuation phase (phase 2). Log-rank test comparing distributions of time to relapse for C-ECT vs C-Pharm: χ^2=0.30; P=.59. C-ECT indicates continuation electroconvulsive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

Treatment Responsive Disorders

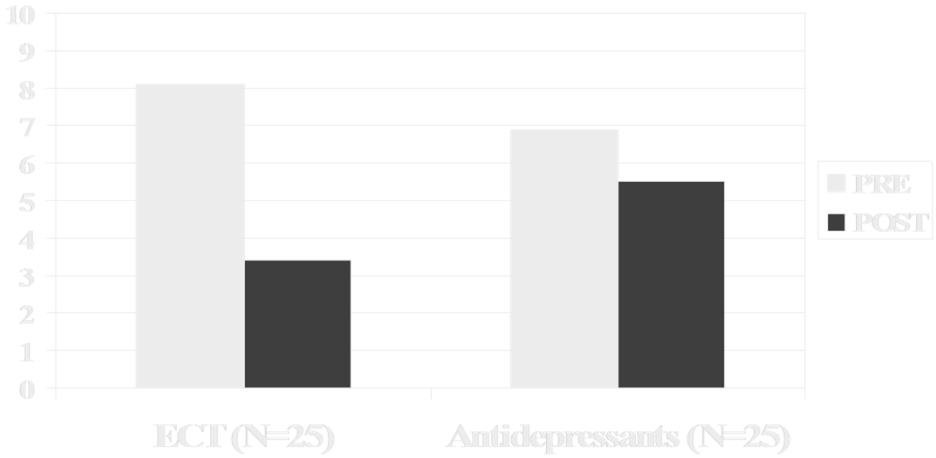
- Major Depressive Illness with or without psychotic features
- Bipolar, depressed
- Bipolar, manic
- Schizoaffective Disorder
- Schizophrenia - acute onset, confusion
- Catatonia
- Parkinson's Disease (bradykinesia, tremor, rigidity, gait disturbance, postural instability)
- Chronic pain associated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

Previous Antidepressant Treatment	% Response to ECT
• Never adequate trial	• 91%
• Failed adequate trial	• 63%

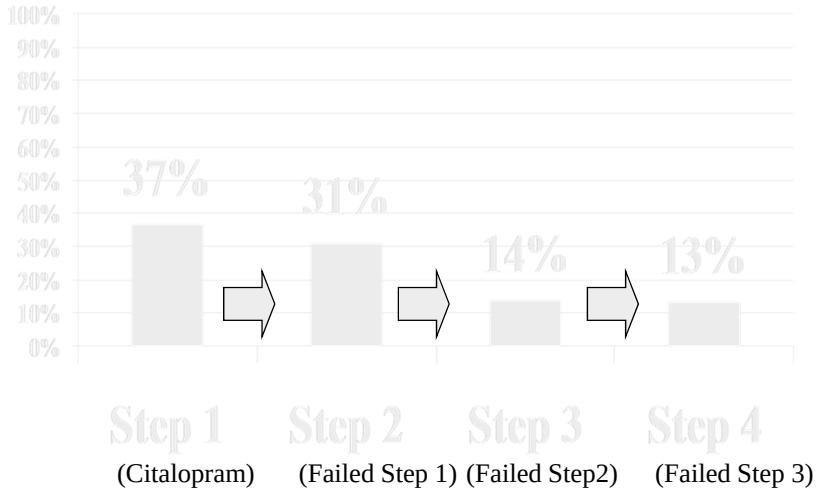
Failure of an adequate trial of hetercyclics (but not SSRIs) was associated with a poor response to Unilateral ECT (Prudic et al, 1996).

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

Consider

- Caffeine
- Atropine
- Labetalol
- Esmolol

Avoid

- Lithium
- Anticonvulsants
  esp. Benzodiazapines
  (Consider Zolpidem for sleep)

Should an Antidepressant Medication be given with ECT?

- ECT response rates significantly better with concomitant antidepressant (venlafaxine or nortriptyline) compared with placebo.
- Sackeim et al, 2008.

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.

ECT	Remission Rate
Bilateral	65%
RUL- 6X	60%
RUL-2.5X	30%
RUL-1.5X	35%

Sackeim et al, 2000

High Dose Right Unilateral ECTas Efficacious as Bitemporal ECT with Less Cognitive Disturbance

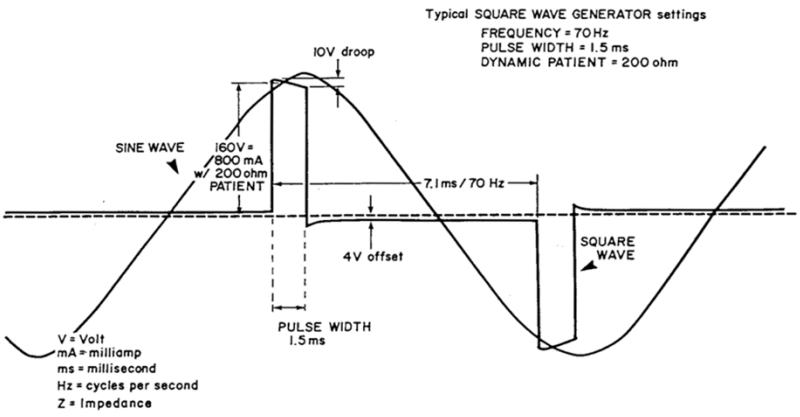
- Abrams et al, 1991(n=38)
- Sackeim et al, 1993(n=96)
- Sackeim et al, 2000(n=80)

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

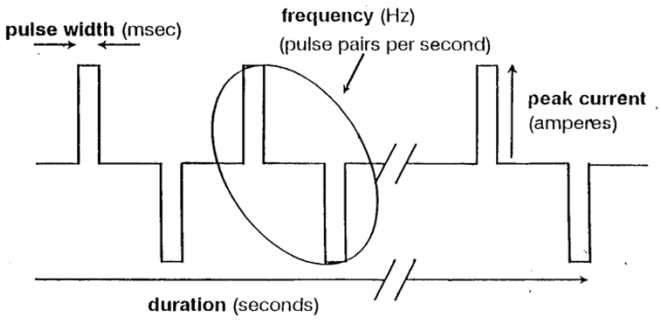
McCall et al, 2000

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) [millicoulombs]

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

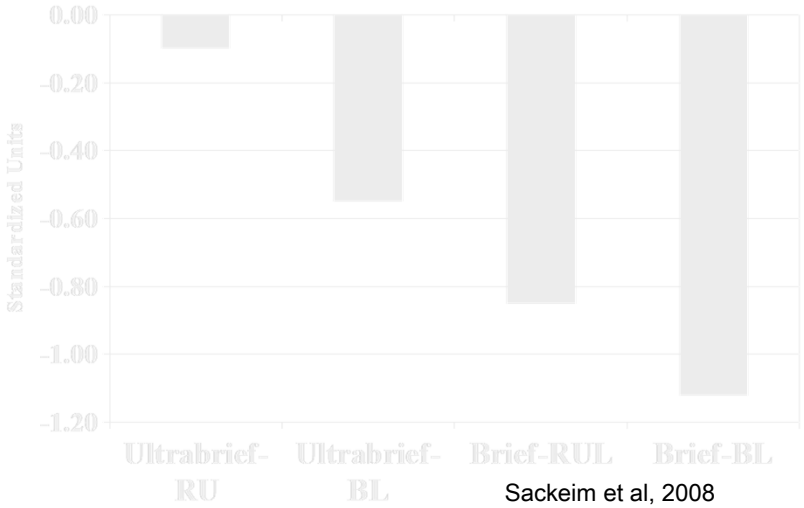
Ultrabrief ECT Study

- 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



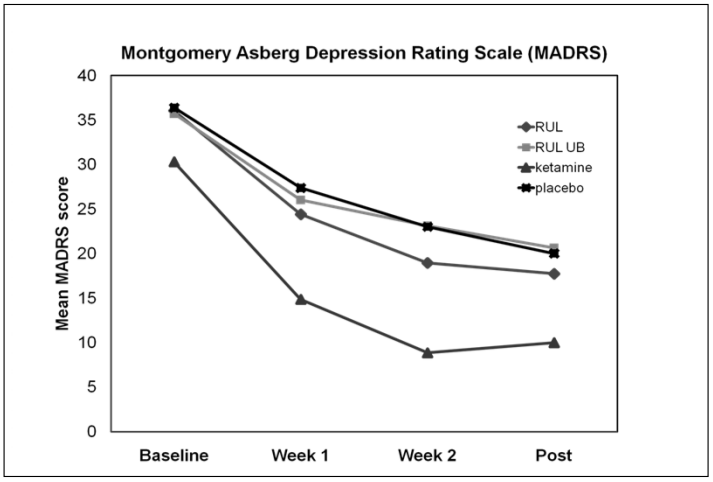
Sackeim et al, 2008

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

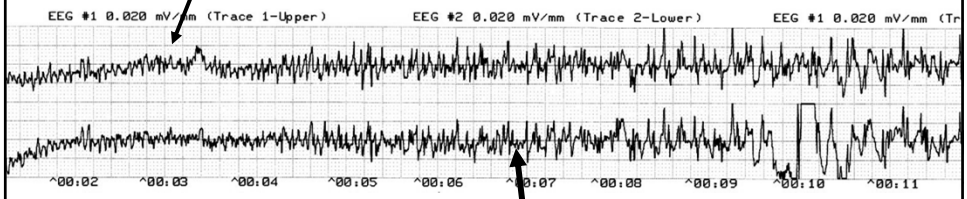


Notes: RUL indicates right unilateral (N = 22); RUL UB, right unilateral ultra brief (N = 78); Ketamine with RUL UB (N = 7); Placebo (N = 8).

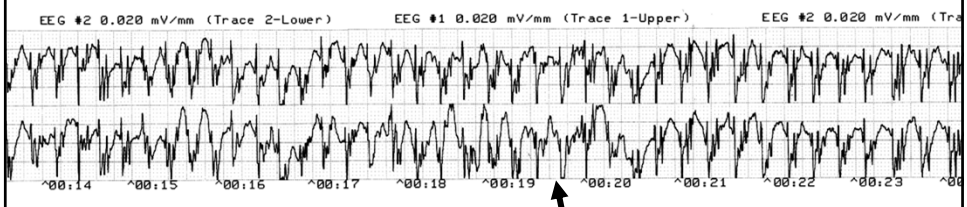
Loo, 2009

The following slides show a typical two lead EEG during an ECT treatment

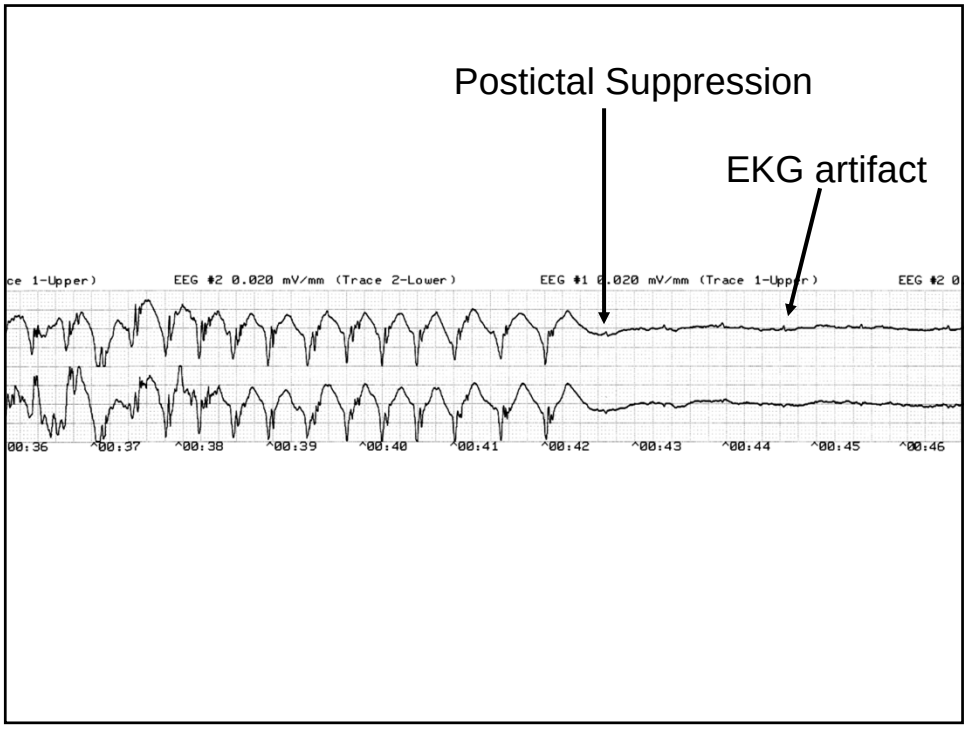
Recruitment



Tonic phase of seizure



Clonic phase of seizure



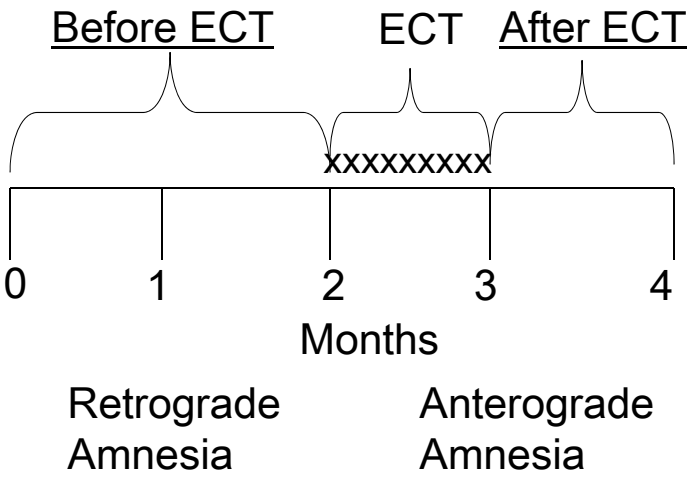
Clinical Response to ECT associated with some EEG characteristics:

- 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



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 nondemented elderly, which has strong clinical relevance concerning the use of ECT. Depression and Anxiety 23:93–101, 2006.

Cognition functions often improve with ECT

TABLE 2. Effect size (η^2) values of cognitive test variable for the significant differences between test sessions for effect of mood improvement or ECT (without covariate), and for effect of ECT (with covariate)

	Differences between test sessions											
	1 and 2[b]				2 and 3		3 and 4		1 and 4			
	Without covariate		With covariate		Without covariate		Without covariate		Without covariate		With covariate	
Cognitive test variable[a]	η^2	*P*	η^2	*P*	η^2	*P*	η^2	*P*	η^2	*P*	η^2	*P*
■ WMS Paired Associates	0.23	0.029	0.23	0.037					0.47	0.019	0.48	0.027
■ 10-word List	0.23	0.029			0.31	0.021						
■ BVRT Correct Responses	0.20	0.048	0.27	0.031								
■ WMS Visual Reproduction									0.39	0.039	0.45	0.034
■ WMS Orientation	0.27	0.017	0.28	0.019	0.25	0.041						
■ MOQ Semantic Recent					0.50	0.033						
■ GIT Word Matrices							0.53	0.017				
■ Stroop Card II speed	0.38	0.007							0.48	0.026	0.48	0.039
■ Stroop Card III speed									0.40	0.048		
■ Stroop Card III faults	0.24	0.037	0.26	0.043								
■ WAIS Digit Symbol	0.28	0.017	0.28	0.024					0.43	0.028	0.47	0.029
■ WMS Mental Control			0.22	0.043								
■ GIT IQ							0.65	0.005				
■ GIT Incomplete Pictures									0.42	0.03	0.56	0.013
■ GIT Visualization							0.65	0.005			0.39	0.05

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

Depression and Anxiety DOI 10.1002/da

Bosboom, 2006

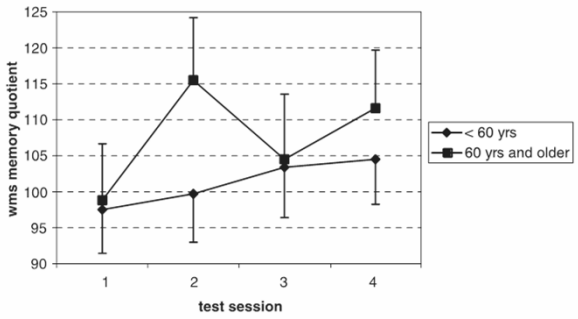


Figure 1. Mean scores [± SEM (standard error of mean)] on the Wechsler Memory Quotient (MQ) for the young and older patient groups at the four test sessions.

Session 1, one week before ECT index;
Dession 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.

Devanand et al, AJP 148:929, 1991

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

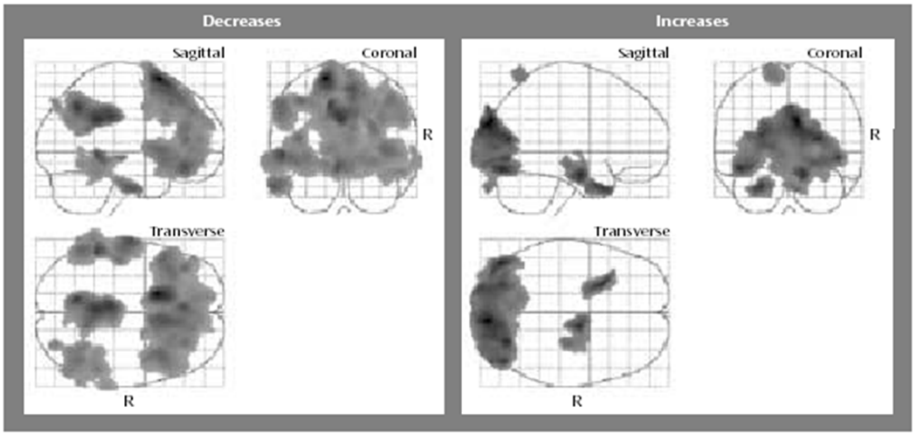
Proposed Mechanisms of Action ECT

- 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.

FIGURE 1. Statistical Maps of Decreases and Increases in Normalized Regional Glucose Metabolism in 10 Patients With Major Depression After a Course of Bilateral ECT[a]



[a] Pixel-by-pixel analyses of changes in regional cerebral metabolic rate for glucose, after control for global glucose metabolic levels. "R" indicates right side. For regions of interest in which decreases were found, peak statistical parametric mapping voxel-level z scores were 5.81 at stereotactic coordinates –14, 16, 68 in the superior frontal lobe ($p<0.001$, df=8, one-tailed), 4.95 at coordinates 0, –42, 32 in the parietal lobe ($p=0.005$, df=8, one-tailed), and 4.65 at coordinates –52, –42, 0 in the left middle temporal lobe ($p<0.02$, df=8, one-tailed).

ECT Seizure Threshold

- Males higher than females.
- Depressed higher than manic.
- Increases with age.
- Increases as the Number of ECT Treatment Increases
- <u>Increases are Related to the Degree of Response to ECT</u>
- 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

Brain Stimulation Approaches To Treatment-Resistant Depression

David Avery, M.D.
Psychiatric Medicine Associates
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University of Washington

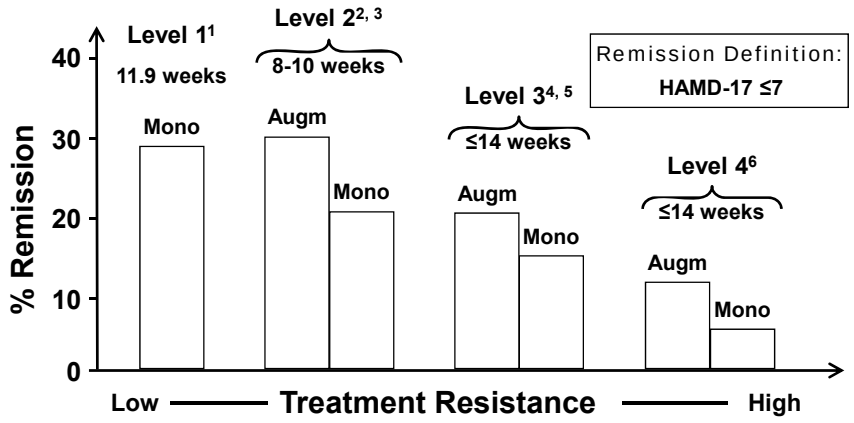
Outline

- 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



Mono = single medication regimen; Augm = combination medication treatment; [1]Trivedi MH et al. (2006), Am J Psychiatry 163:28-40; [2]Trivedi MH et al. (2006), N Engl J Med 354:1243-1252; [3]Rush AJ et al. (2006), N Engl J Med 354:1231-1242; [4]Nierenberg AA et al. (2006), Am J Psychiatry 163:1519-1530; [5]Fava M et al. (2006), Am J Psychiatry 163:1161-1172; [6]McGrath 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)

Trial	Number of participants	Standardised effect size (95% CI)
Wilson 1963[10]	12	−1·078 (−2·289 to 0·133)
West 1981[11]	25	−1·255 (−2·170 to −0·341)
Lambourn 1978[15]	40	−0·170 (−0·940 to 0·600)
Freeman 1978[12]	40	−0·629 (−1·264 to 0·006)
Gregory 1985[13]	69	−1·418 (−2·012 to −0·824)
Johnstone 1980[14]	70	−0·739 (−1·253 to −0·224)
Pooled fixed effects		−0·911 (−1·180 to −0·645)
Pooled random effects		−0·908 (−1·270 to −0·537)

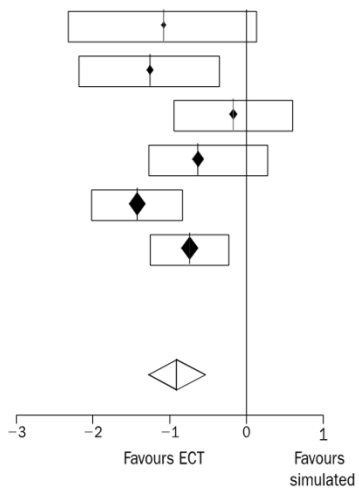


Figure 1: **Effect of ECT versus simulated ECT on depressive symptoms**

ECT vs Pharmacotherapy (UK Review Group, 2003)

Trial*	Number of participants	Standardised effect size (95% CI)
Steiner 1978[16]	12	0·369 (–0·840 to 1·578)
Wilson 1963[10]	12	–0·513 (–1·663 to 0·637)
Davidson 1978[17]	19	–1·389 (–2·449 to –0·328)
McDonald 1966[18]	22	–0·930 (–1·813 to –0·047)
Gangadhar 1982[19]	32	1·287 (0·406 to 2·169)
MacSweeney 1975[20]	27	–0·714 (–1·492 to 0·065)
Dinan 1989[21]	30	–0·196 (–0·926 to 0·534)
Janakiramaiah 2000[22]	30	–1·095 (–1·863 to –0·328)
Folkerts 1997[23]	40	–1·336 (–2·032 to –0·640)
Herrington 1974[24]	43	–1·497 (–2·174 to –0·821)
Stanley 1962[25]	47	–1·342 (–2·047 to –0·638)
Medical Research Council 1965[26]	204	–0·559 (–0·883 to –0·234)
Greenblatt 1964[27]	242	–1·683 (–2·020 to –1·346)
Pooled fixed effects		–1·010 (–1·170 to –0·856)
Pooled random effects		–0·802 (–1·290 to –0·289)

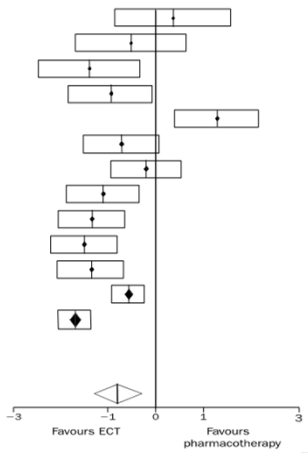


Figure 3: **Effect of ECT versus pharmacotherapy on depressive symptoms**
*Other trials not included: Kendrick 1965,[28] Bruce 1960,[29] Bagadia 1981,[30] Hutchinson 1963,[31] Robin 1962.[32]

Bitemporal vs Unilateral ECT (UK Review Group, 2003)

Trial*	Number of participants	Standardised effect size (95% CI)
Abrams 1969[33]	21	0·017 (–0·840 to 0·873)
Valentine 1968[34]	24	0·076 (–0·724 to 0·877)
Fraser 1980[35]	33	–0·320 (–1·057 to 0·416)
Abrams 1974[36]	30	0·082 (–0·678 to 0·841)
Costello 1970[37]	30	–0·342 (–1·106 to 0·422)
Fleminger 1970[38]	36	–0·317 (–1·013 to 0·380)
Taylor 1985[39]	37	–0·951 (–1·642 to –0·260)
Abrams 1991[40]	38	–0·544 (–1·192 to 0·105)
Gregory 1985[13]	46	0·215 (–0·407 to 0·837)
Levy 1968[41]	40	–0·200 (0·821 to 0·422)
Martin 1965[42]	40	0·111 (–0·510 to 0·731)
Carney 1976[43]	45	–0·188 (–0·781 to 0·404)
Horne 1985[44]	48	–0·183 (–0·750 to 0·384)
Abrams 1983[45]	70	–0·565 (–1·125 to –0·004)
Halliday 1968[46]	52	–0·171 (–0·743 to 0·401)
Sackeim 1987[48]	52	–0·818 (–1·385 to –0·252)
Malitz 1986[47]	52	–0·835 (–1·402 to –0·268)
Letemendia 1993[49]	83	–0·383 (–0·951 to 0·185)
D'Elia 1970[50]	59	–0·068 (–0·579 to 0·442)
Sackeim 2000[51]	84	–0·830 (–1·352 to –0·308)
Sackeim 1993[52]	100	–0·694 (–1·106 to –0·281)
Stromgren 1973[53]	117	–0·086 (–0·479 to 0·306)
Pooled fixed effects		–0·323 (–0·446 to –0·199)
Pooled random effects		–0·322 (–0·458 to –0·186)

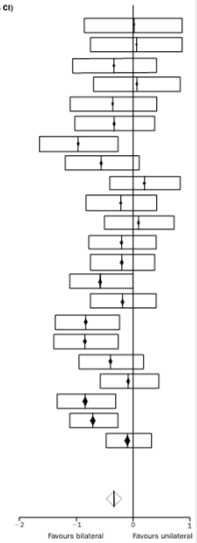


Figure 5: **Effect of bilateral versus unilateral electrode placement on depressive symptoms**
*Other trials not included: Welch 1982,[54] Papalkostas 1994,[55] Krystal 1992,[56] Daniel 1984,[57] Heshe 1978,[58] Bidder 1970.[59]

1X per week ECT vs 3X per week
2X per week ECT vs 3X per week
(UK Review Group, 2003)

Trial	Number of participants	Standardised effect size (95% CI)
Once a week *vs* three times a week		
Kellner 1992[65]	11	0·504 (−0·526 to 1·534)
Janakiramaiah 1998[66]	40	0·940 (0·287 to 1·593)
Pooled fixed effects		0·841 (0·311 to 1·370)
Pooled random effects		0·832 (−0·389 to 1·890)
Twice a week *vs* three times a week		
Gangadhar 1993[67]	30	−0·293 (−1·013 to 0·426)
Shapira 1998[68]	31	0·123 (−0·585 to 0·831)
Vieweg 1998[70]	46	−0·888 (−1·530 to −0·246)
Lerer 1995[69]	52	0·049 (−0·523 to 0·621)
Pooled fixed effects		−0·308 (−0·629 to 0·014)
Pooled random effects		−0·299 (−0·759 to 0·199)

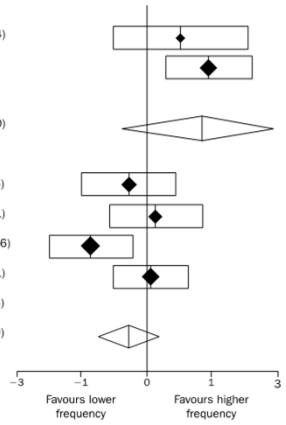


Figure 6: **Effect of frequency of ECT on depressive symptoms**

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

Trial*	Number of participants	Standardised effect size (95% CI)
McCall 1995[71]	22	0·829 (–0·042 to 1·700)
Warren 1998[73]	23	1·218 (0·463 to 1·974)
Janakiramaiah 1984[66]	40	0·273 (–0·349 to 0·896)
McCall 2000[72]	72	0·389 (–0·078 to 0·855)
Sackeim 2000[51]	80	0·368 (–0·141 to 0·877)
Sackeim 1993[52]	100	0·650 (0·239 to 1·061)
Pooled fixed effects		0·571 (0·352 to 0·790)
Pooled random effects		0·575 (0·329 to 0·829)

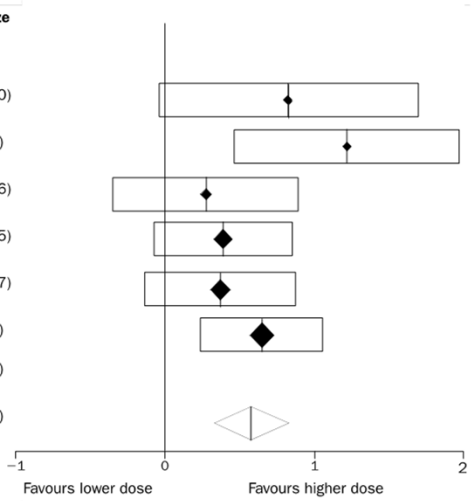


Figure 7: **Effect of higher versus lower dose of ECT on depressive symptoms**
*Other trials not included: Krystal 1996.[74]

ECT is equally effective
in treating unipolar depression and bipolar depression.

Dierckx et al, 2012

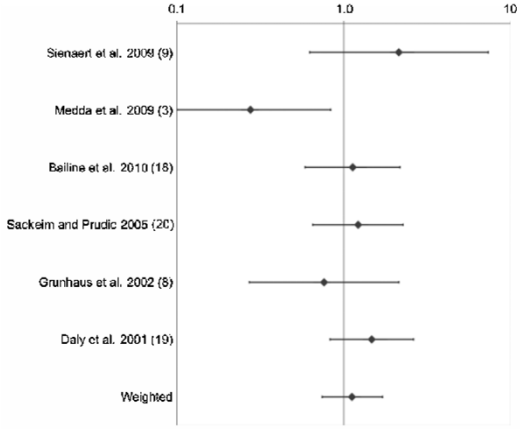


Fig. 1. Plot of the odds ratios of response to electroconvulsive therapy in patients with unipolar versus bipolar depression per study, with 95% confidence interval, after natural logarithmic transformation.

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.

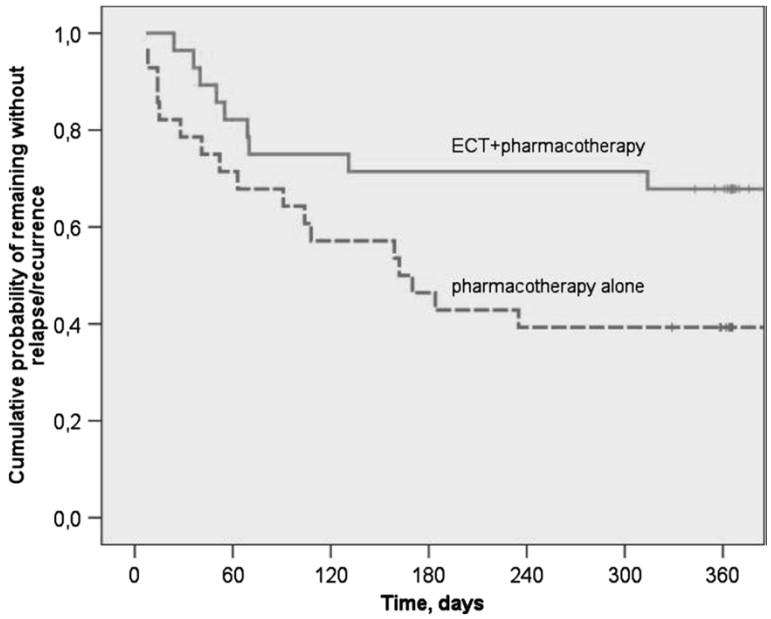


FIGURE 2. Kaplan-Meier function of the cumulative probability of remaining without relapse for patients treated with continuation ECT plus pharmacotherapy versus pharmacotherapy-alone in the intention-to-treat sample.

Nordenskjold, 2013

Continuation ECT vs Continuation Pharmacotherapy

Kellner 2006

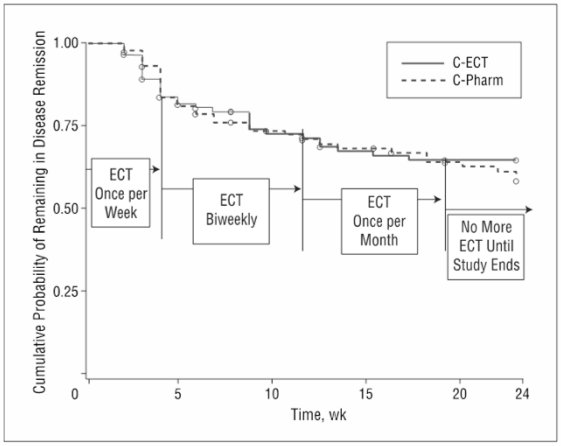


Figure 2. Kaplan-Meier curves showing proportion of patients who remained in disease remission (not disease relapse) during the continuation phase (phase 2). Log-rank test comparing distributions of time to relapse for C-ECT vs C-Pharm: χ^2=0.30; P=.59. C-ECT indicates continuation electroconvulsive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

Treatment Responsive Disorders

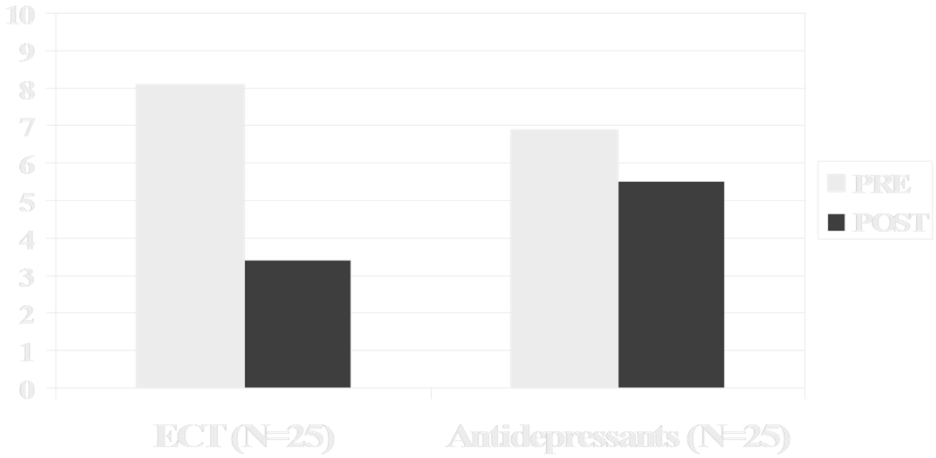
- Major Depressive Illness with or without psychotic features
- Bipolar, depressed
- Bipolar, manic
- Schizoaffective Disorder
- Schizophrenia - acute onset, confusion
- Catatonia
- Parkinson's Disease (bradykinesia, tremor, rigidity, gait disturbance, postural instability)
- Chronic pain associated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

Previous Antidepressant Treatment	% Response to ECT
• Never adequate trial	• 91%
• Failed adequate trial	• 63%

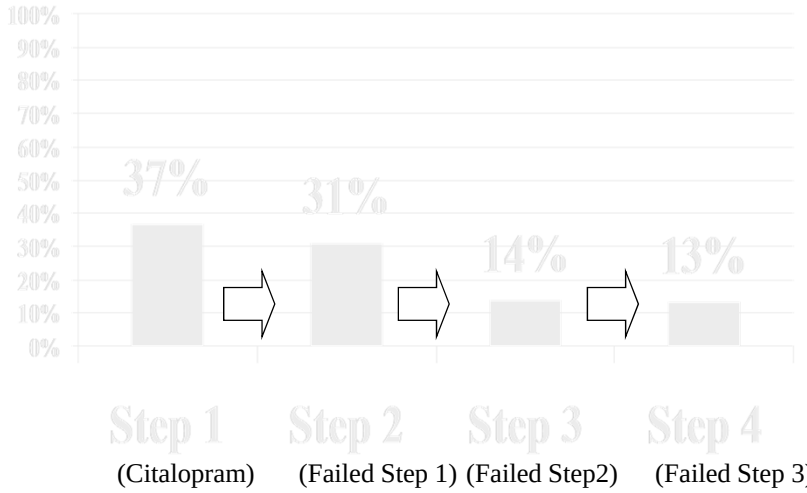
Failure of an adequate trial of hetercyclics (but not SSRIs) was associated with a poor response to Unilateral ECT (Prudic et al, 1996).

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

Consider

- Caffeine
- Atropine
- Labetalol
- Esmolol

Avoid

- Lithium
- Anticonvulsants
  esp. Benzodiazapines
  (Consider Zolpidem for sleep)

Should an Antidepressant Medication be given with ECT?

- ECT response rates significantly better with concomitant antidepressant (venlafaxine or nortriptyline) compared with placebo.
- Sackeim et al, 2008.

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.

ECT	Remission Rate
Bilateral	65%
RUL- 6X	60%
RUL-2.5X	30%
RUL-1.5X	35%

Sackeim et al, 2000

High Dose Right Unilateral ECTas Efficacious as Bitemporal ECT with Less Cognitive Disturbance

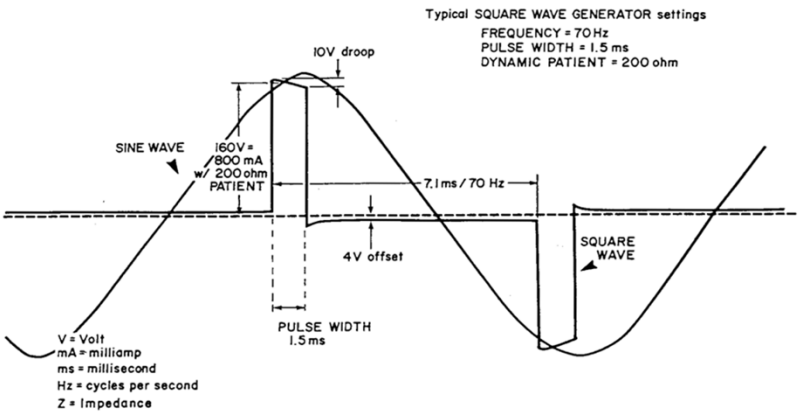
- Abrams et al, 1991(n=38)
- Sackeim et al, 1993(n=96)
- Sackeim et al, 2000(n=80)

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

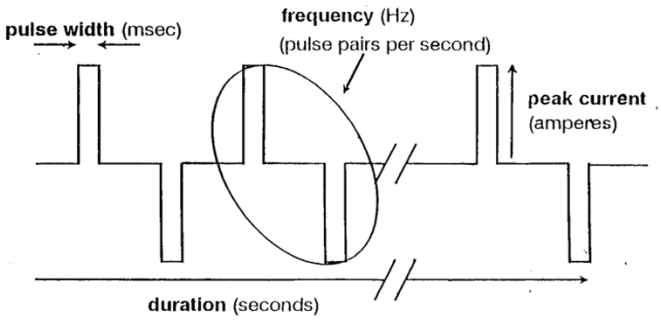
McCall et al, 2000

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) [millicoulombs]

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

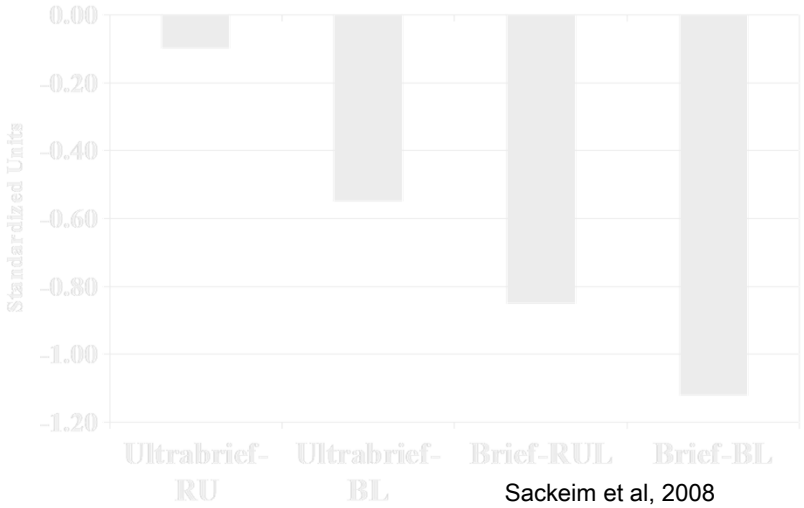
Ultrabrief ECT Study

- 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



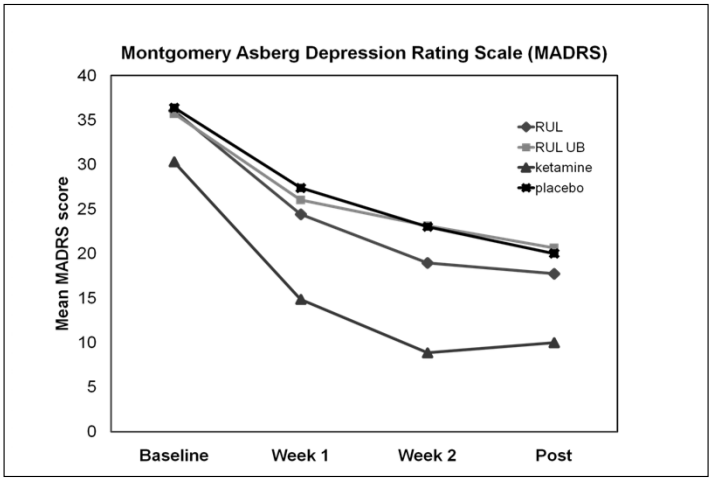
Sackeim et al, 2008

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

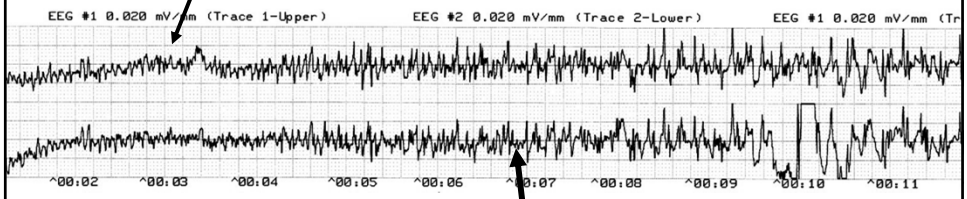


Notes: RUL indicates right unilateral (N = 22); RUL UB, right unilateral ultra brief (N = 78); Ketamine with RUL UB (N = 7); Placebo (N = 8).

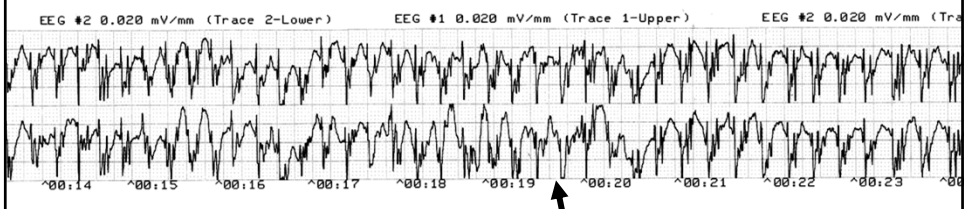
Loo, 2009

The following slides show a typical two lead EEG during an ECT treatment

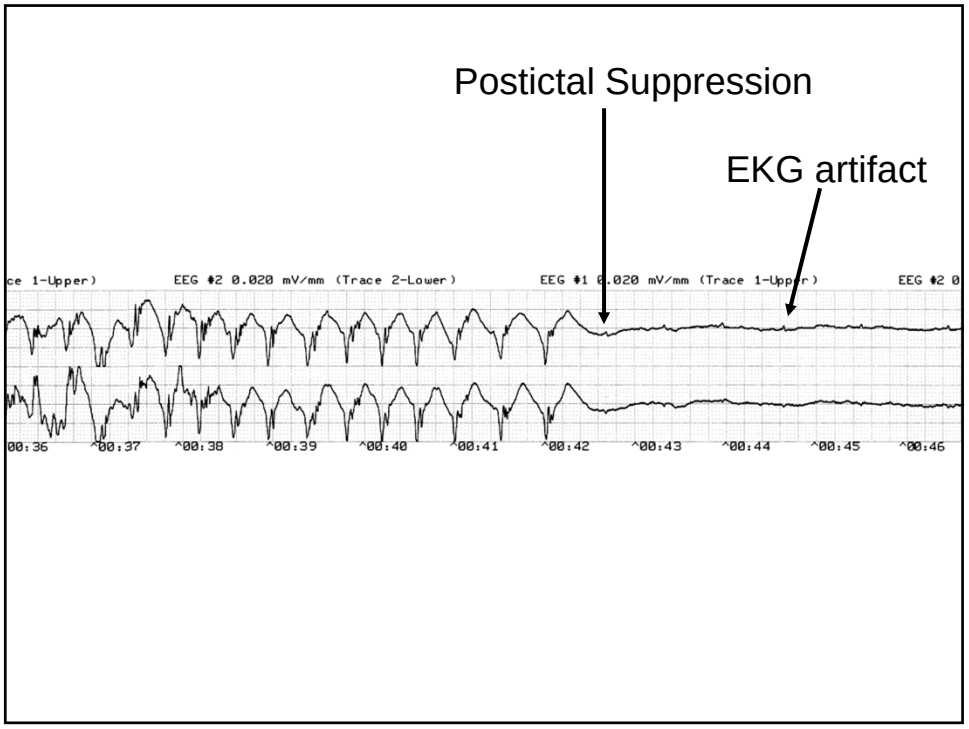
Recruitment



Tonic phase of seizure



Clonic phase of seizure



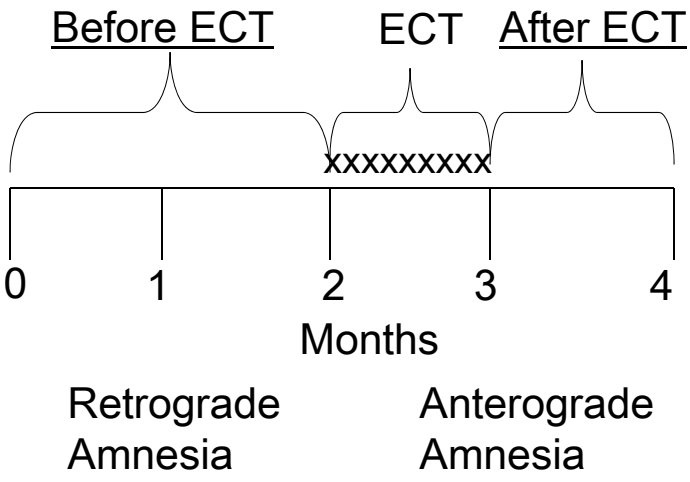
Clinical Response to ECT associated with some EEG characteristics:

- 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



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 nondemented elderly, which has strong clinical relevance concerning the use of ECT. Depression and Anxiety 23:93–101, 2006.

Cognition functions often improve with ECT

TABLE 2. Effect size (η^2) values of cognitive test variable for the significant differences between test sessions for effect of mood improvement or ECT (without covariate), and for effect of ECT (with covariate)

	Differences between test sessions											
	1 and 2[b]				2 and 3		3 and 4		1 and 4			
	Without covariate		With covariate		Without covariate		Without covariate		Without covariate		With covariate	
Cognitive test variable[a]	η^2	*P*	η^2	*P*	η^2	*P*	η^2	*P*	η^2	*P*	η^2	*P*
■ WMS Paired Associates	0.23	0.029	0.23	0.037					0.47	0.019	0.48	0.027
■ 10-word List	0.23	0.029			0.31	0.021						
■ BVRT Correct Responses	0.20	0.048	0.27	0.031								
■ WMS Visual Reproduction									0.39	0.039	0.45	0.034
■ WMS Orientation	0.27	0.017	0.28	0.019	0.25	0.041						
■ MOQ Semantic Recent					0.50	0.033						
■ GIT Word Matrices							0.53	0.017				
■ Stroop Card II speed	0.38	0.007							0.48	0.026	0.48	0.039
■ Stroop Card III speed									0.40	0.048		
■ Stroop Card III faults	0.24	0.037	0.26	0.043								
■ WAIS Digit Symbol	0.28	0.017	0.28	0.024					0.43	0.028	0.47	0.029
■ WMS Mental Control			0.22	0.043								
■ GIT IQ							0.65	0.005				
■ GIT Incomplete Pictures									0.42	0.03	0.56	0.013
■ GIT Visualization							0.65	0.005			0.39	0.05

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

Depression and Anxiety DOI 10.1002/da

Bosboom, 2006

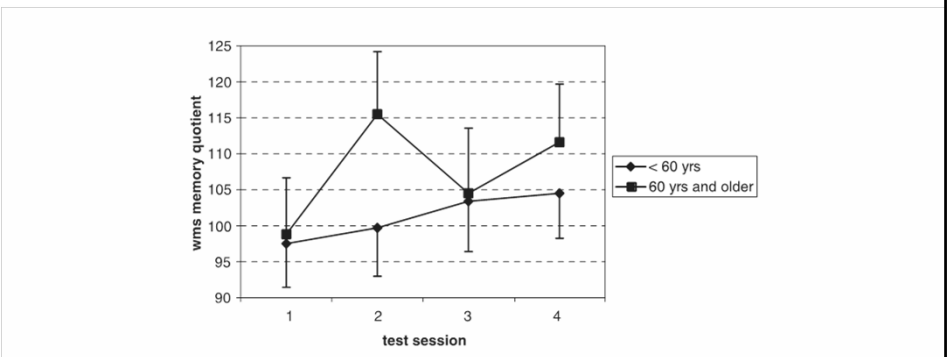


Figure 1. Mean scores [± SEM (standard error of mean)] on the Wechsler Memory Quotient (MQ) for the young and older patient groups at the four test sessions.

Session 1, one week before ECT index;
Dession 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.

Devanand et al, AJP 148:929, 1991

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

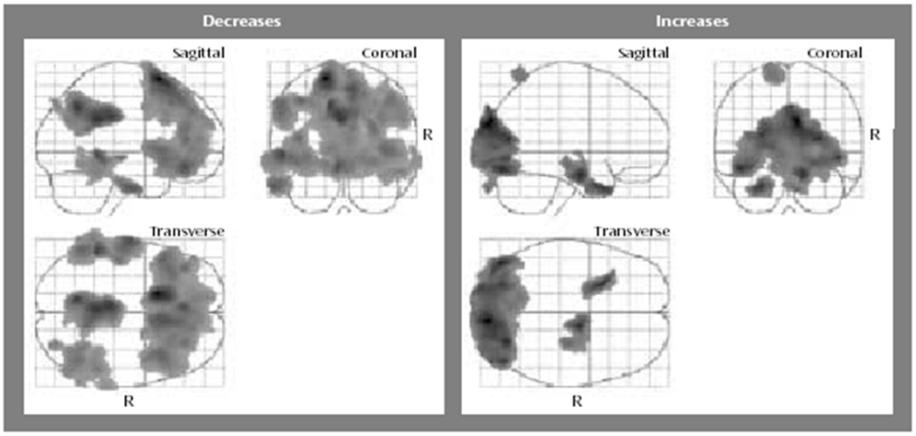
Proposed Mechanisms of Action ECT

- 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.

FIGURE 1. Statistical Maps of Decreases and Increases in Normalized Regional Glucose Metabolism in 10 Patients With Major Depression After a Course of Bilateral ECT[a]



[a] Pixel-by-pixel analyses of changes in regional cerebral metabolic rate for glucose, after control for global glucose metabolic levels. "R" indicates right side. For regions of interest in which decreases were found, peak statistical parametric mapping voxel-level z scores were 5.81 at stereotactic coordinates –14, 16, 68 in the superior frontal lobe ($p<0.001$, df=8, one-tailed), 4.95 at coordinates 0, –42, 32 in the parietal lobe ($p=0.005$, df=8, one-tailed), and 4.65 at coordinates –52, –42, 0 in the left middle temporal lobe ($p<0.02$, df=8, one-tailed).

ECT Seizure Threshold

- Males higher than females.
- Depressed higher than manic.
- Increases with age.
- Increases as the Number of ECT Treatment Increases
- <u>Increases are Related to the Degree of Response to ECT</u>
- 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)

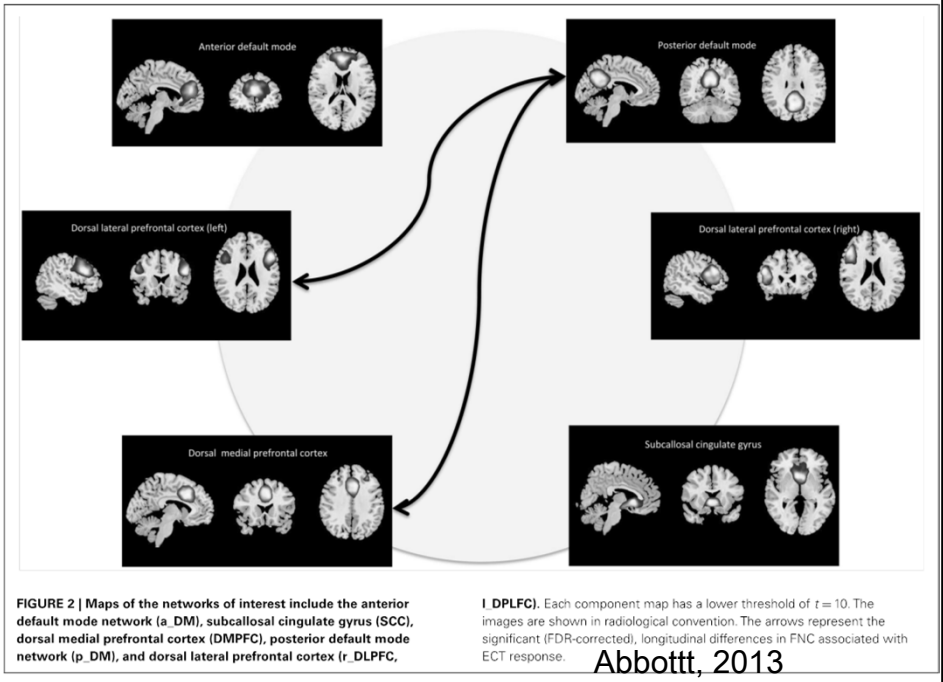


FIGURE 2 | Maps of the networks of interest include the anterior default mode network (a_DM), subcallosal cingulate gyrus (SCC), dorsal medial prefrontal cortex (DMPFC), posterior default mode network (p_DM), and dorsal lateral prefrontal cortex (r_DLPFC, l_DPLFC). Each component map has a lower threshold of $t = 10$. The images are shown in radiological convention. The arrows represent the significant (FDR-corrected), longitudinal differences in FNC associated with ECT response.

Abbottt, 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.

Beall, 2012

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

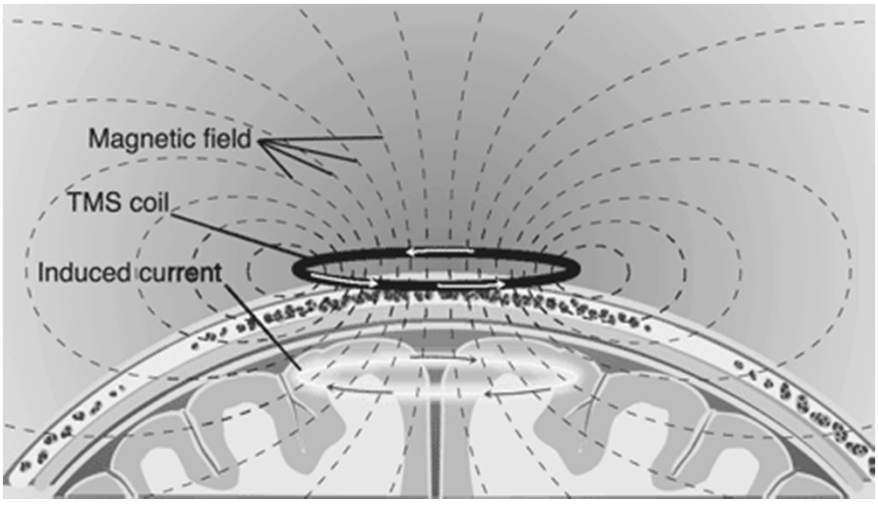
Perrin, 2012

Main Points

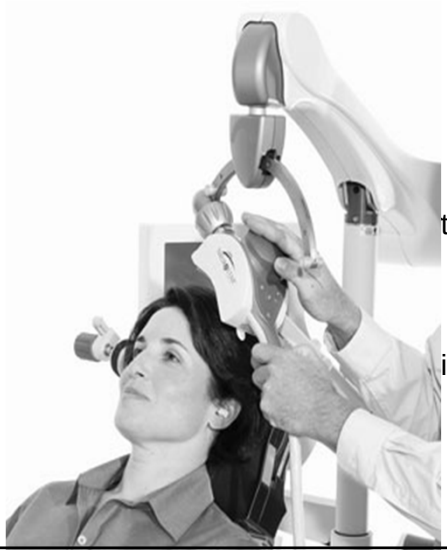
- Medication-Resistance Depression is common and usually has poor response rates to further antidepressant trials; ECT is usually effective in this population.
- Ultra-Brief Right Unilateral ECT is very effective and has minimal memory disturbance.
- ECT increases neuroplasticity and changes the connectivity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



TMS



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

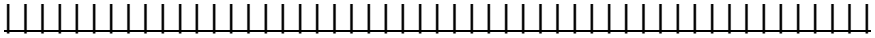
- Using multiple capacitors, rTMS machines are able to deliver regular repeated pulses to a single scalp site.
- rTMS may have sustained effects.

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

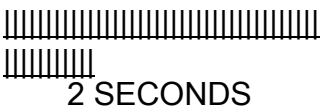
10 and 20 Hz rTMS Trains of 100 Microsecond Pulses

10 Hz x 5 Seconds, 32 Trains per session, 15 sessior



5 SECONDS

20 Hz x 2 Seconds, 20 Trains per session, 10 sessio



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

	ECT	rTMS
Charge Density (microcoulombs/cm2)	20	1-2
Stimulus	Diffuse	Focal
Memory Disturbance	Yes	No
Post-Ictal Confusion	Yes	No
Anesthesia	Yes	No

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

	ECT	rTMS
• Beta-Adrenergic Receptors Down-regulated	+	+
• Apomorphine Stereotopy Increased	+	+
• Porsolt Swim Test	+	+
• Increases Seizure Threshold	+	+

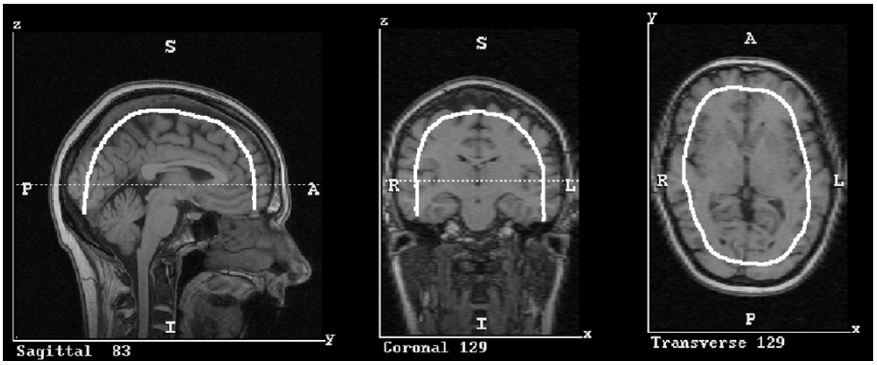
Possible mechanisms of action

- 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

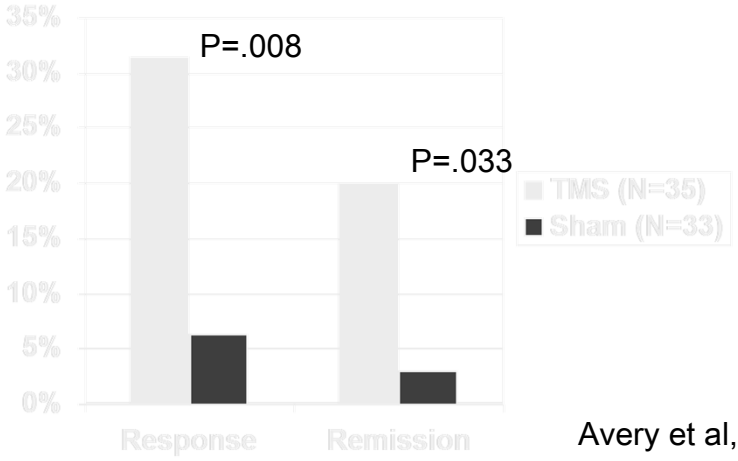
Approximate Depth Limit of Direct Stimulation With Current TMS Coils



TMS has <u>indirect</u> 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 <u>and</u> contralateral motor cortex shows increases in fMRI activity.

Response (50% or more decrease in HAMD)
and Remission (HAMD <8)
in TMS and Sham Groups



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 literature[1-3]

FDA approval for TMS in MDD in 2008 based on results of industry-sponsored, large sample (n=301)RCT[4]

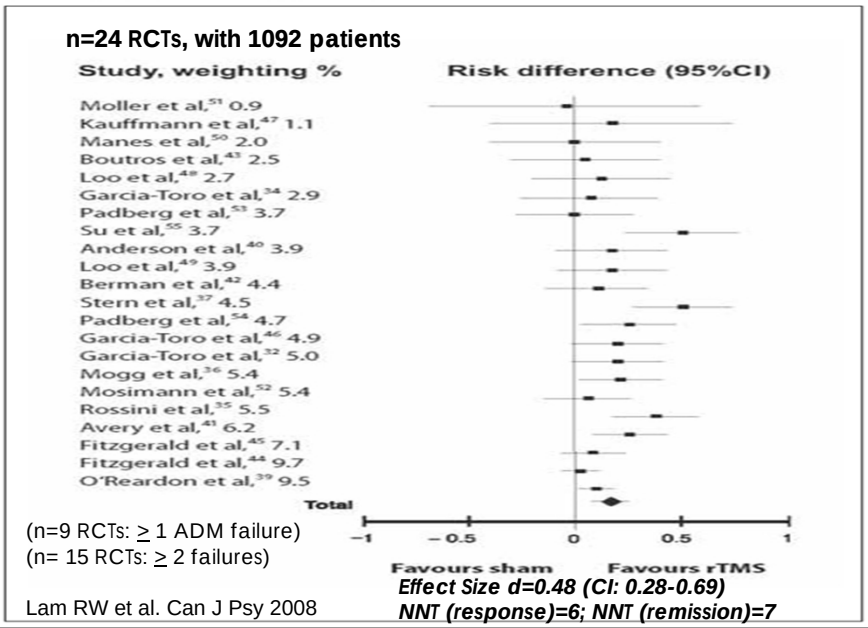
Now have an independent replication in an NIH sponsored (n=199) RCT[5]

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

1. Schutter Psy Med 2008 2. Lam et al. Can J Psy 2008 3. Slotema et al., J.Clin. Psych. 2010
4. O'Reardon et al. Bio Psy 2007 5. George et al. Arch Gen Psy 2010

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

Lam RW et al. Can J Psy 2008

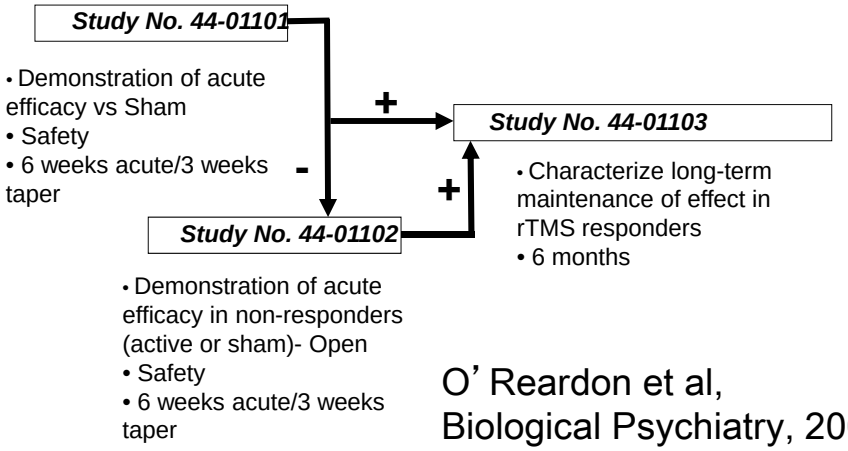
Slow Frequency TMS metaanalysis (2010)

(9 RCTs, 252 patients, 1 Hz to right PFC)	
Active TMS n=134	**Sham TMS n=118**
Effect Size = 0.63 (CI:0.03 – 1.24)	

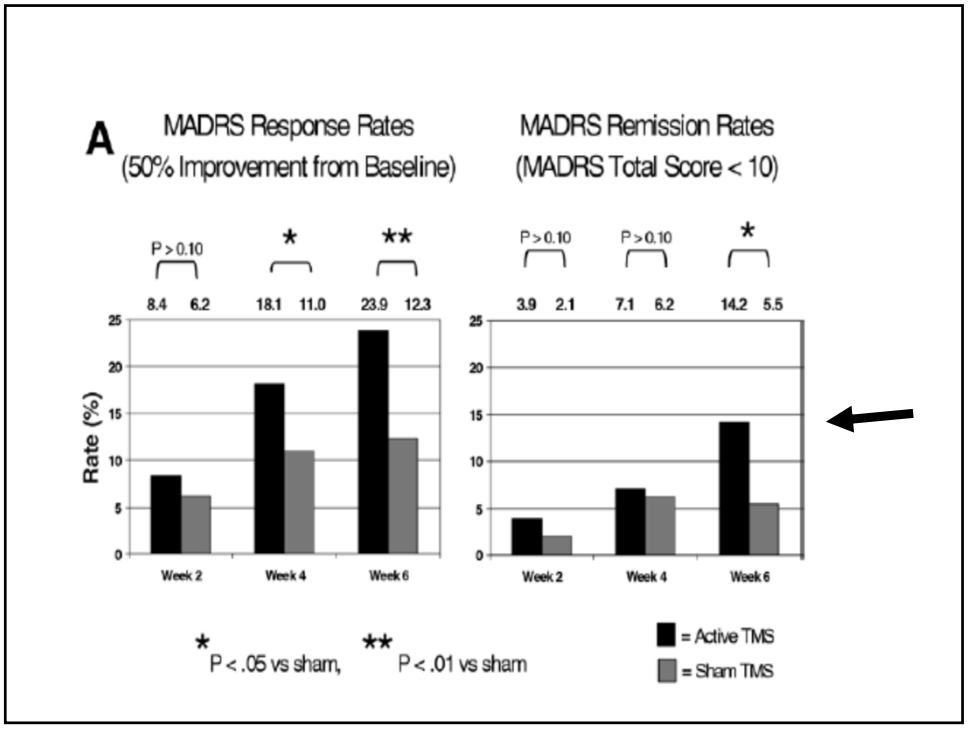
Schutter DJLG Psychol Med 2010

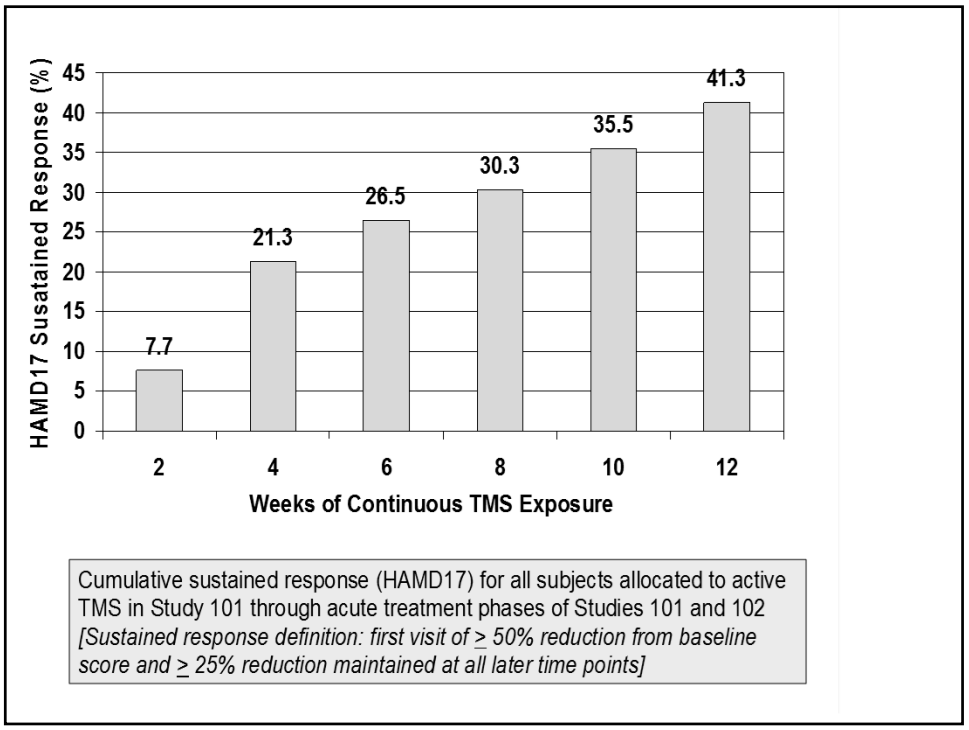
87

Neuronetics TMS Studies N=301



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]

Adverse Events Experienced During Acute Treatment with Active TMS in Study 1

Adverse Event, N (%)	Sham TMS (N=158)	Active TMS (N= 165)
Eye Pain	3 (1.9)	10 (6.1)
Toothache	1 (0.6)	12 (7.3)
Application Site Discomfort	2 (1.3)	18 (10.9)
Application Site Pain	6 (3.8)	59 (35.8)
Facial Pain	5 (3.2)	11 (6.7)
Muscle Twitching	5 (3.2)	34 (20.6)
Pain of Skin	1 (0.6)	14 (8.5)

Adverse events experienced at a rate of ≥ 5% and at least twice that of sham TMS

Janicak PG, et al. *J Clin Psychiatry* 2008;69:222-232

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) reachieved symptom benefits from TMS.
- Relapse Rate = 13%

(vs 40% relapse rate in STAR-D remitters – one previous antidepressant failure)

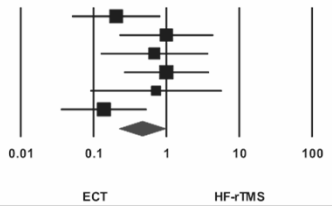
(vs a mean of 23% relapse rate in antidepressant continuation studies.)

(vs ECT + pharmacotherapy, 32% relapse rate;
or ECT continuation ECT, 37%)

Janicak et al, 2010

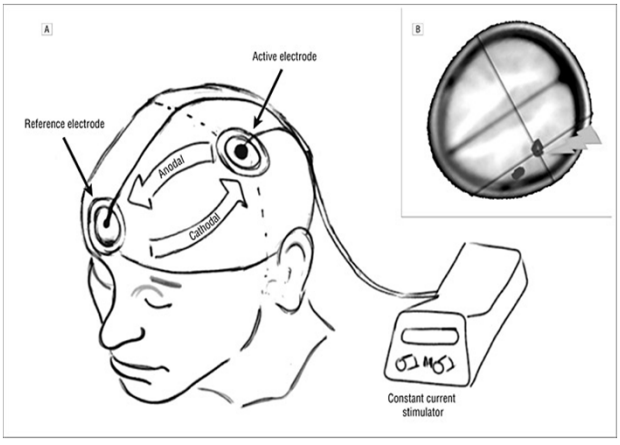
TMS is less effective than ECT, particularly in treating psychotic depresion

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	rTMS	ECT	Relative weight
Grunhaus et al, 2000	0.205	0.050	0.834	-2.212	0.027	9 / 20	16 / 20	18.84
Pridmore et al, 2000	1.000	0.224	4.459	0.000	1.000	11 / 16	11 / 16	17.28
Janicak et al, 2002	0.686	0.124	3.784	-0.433	0.665	6 / 13	5 / 9	14.19
Grunhaus et al, 2003	1.000	0.259	3.867	0.000	1.000	6 / 20	6 / 20	19.85
Rosa et al, 2006	0.722	0.090	5.814	-0.306	0.760	2 / 20	2 / 15	10.31
Eranti et al, 2007	0.138	0.035	0.544	-2.830	0.005	4 / 24	13 / 22	19.53
	0.462	0.221	0.964	-2.057	0.040	38 / 113	53 / 102	



Berlim et al, 2013

Transcranial Direct Current Stimulation



Exp Neurol. 2009 Sep;219(1)

Transcranial Direct Current Stimulation (tDCS) in Major Depression

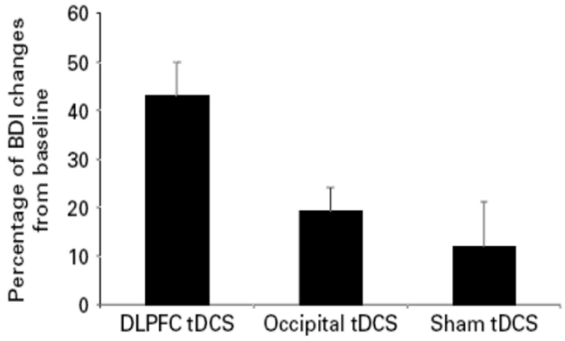


Figure 2. Depression scores changes immediately after 10 d of stimulation compared with baseline in the three groups of treatment. Each column represents mean Hamilton Depression Rating Scale (HDRS) score reduction; error bars indicate S.E.M.

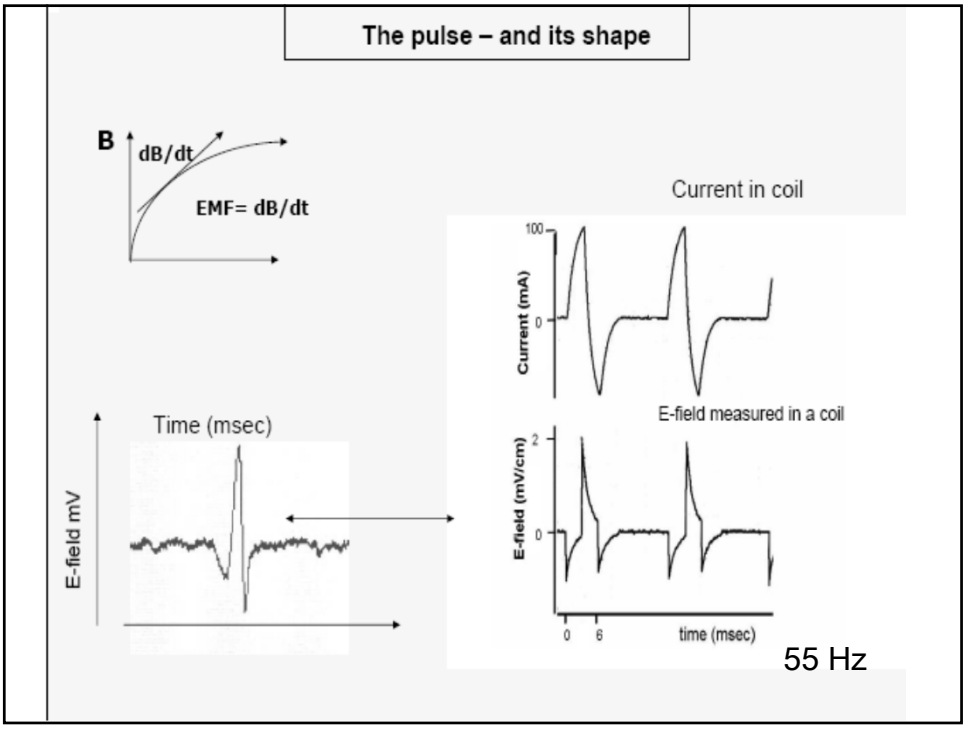
Boggio, 2008

Nitsche, 2009

Transcranial Pulsed Electromagnetic Field (PEMF) Treatment: Maximum 1.9 Gauss (1.9 milliTesla) at .5 cm

ECT vs TMS vs PEMF:
Physics

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



ECT vs TMS vs PEMF: Clinical Administration

	ECT	TMS	PEMF
Generalized Seizure?	Yes	No	**No**
Muscle Relaxant?	Yes	No	**No**
Anesthesia?	Yes	No	**No**
Anesthesiologist?	Yes	No	**No**

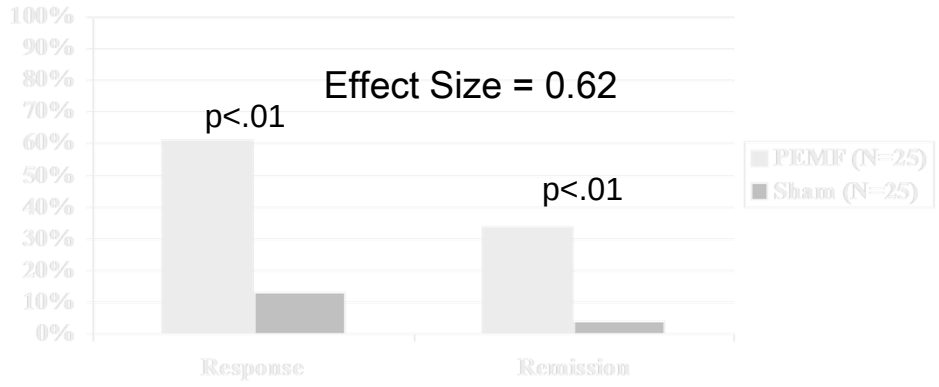
ECT vs TMS vs PEMF: Side Effects and Clinical Administration

	ECT	TMS	PEMF
Exclusion for metal in body?	No	Yes	**No**
Seizure Risk?	Seizure Intended	Yes	**No**
Memory Disturbance?	Yes	No	**No**
Self-Administered?	No	No	**Yes**
Administered in home?	No	No	**Yes**
Cost ++++	Cost ++++	Cost +++	**Cost +**

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 Enironmental 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

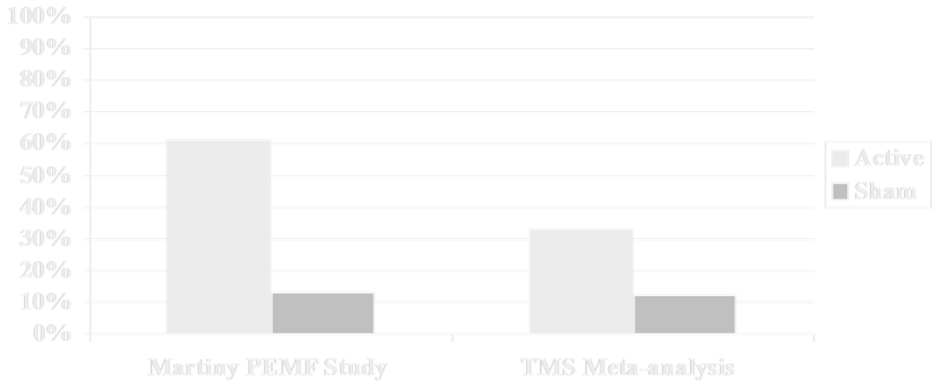


Martiny et al, Biol. Psych, 2010

ECT vs TMS vs PEMF:
Efficacy in Depression

	ECT	TMS	PEMF
Antidepressant Effect Size (d)	0.91	0.39, 0.48, 0.55	**.62**

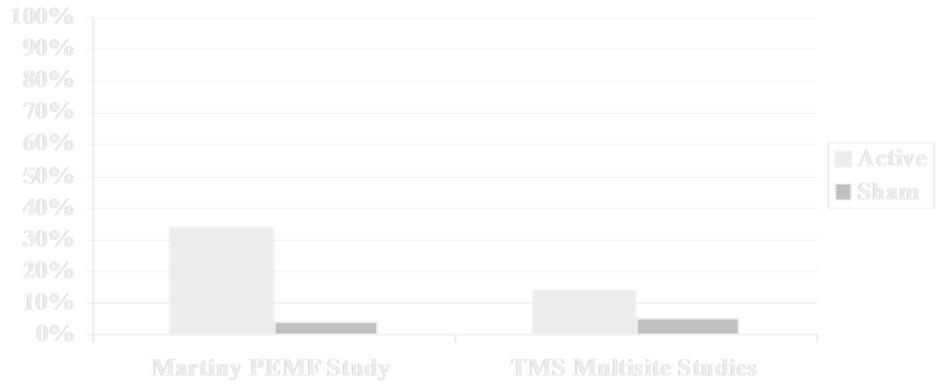
Response Rates in PEMF Study
and Mean Response Rates
in the TMS Meta-analysis (N=1107)



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)

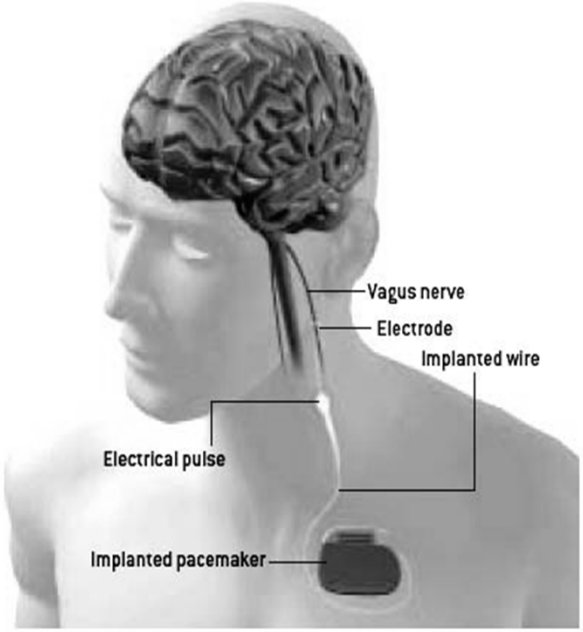


Martiny et al, 2010 George et al, 2010; O'Reardon, 2007

Rationale for Investigating VNS in Depression

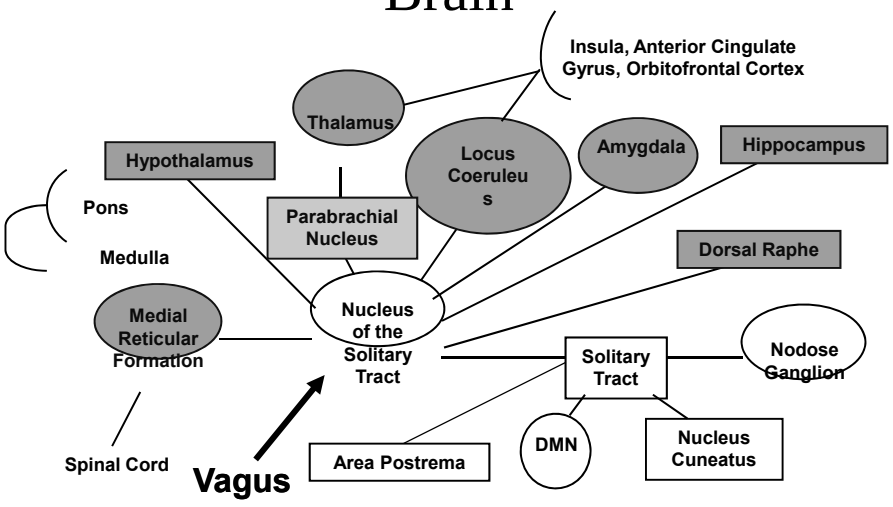
- Long-standing use of VNS to access limbic structures for research
- Known neuroanatomic vagus projections
- PET scans and animal c-fos data showing VNS effects in mood-regulating regions
- Mood effects in VNS patients with epilepsy
- Use of anticonvulsants as mood stabilizers
- Neurochemical and monoamine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

Vagus Nerve Stimulation



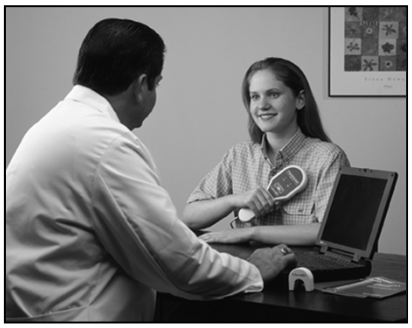
Direct electrical excitation of the vagus nerve in the neck can suppress the onset of brain seizures.

VNS: Afferent Pathway to the Brain



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

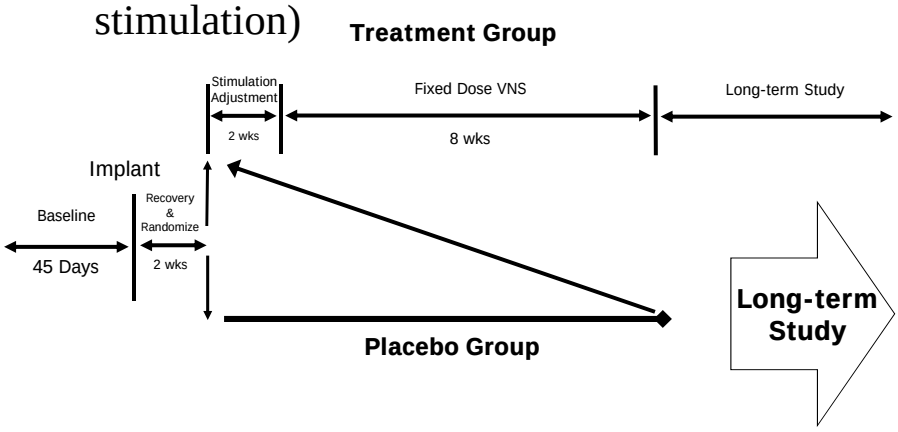
D-02 Study

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

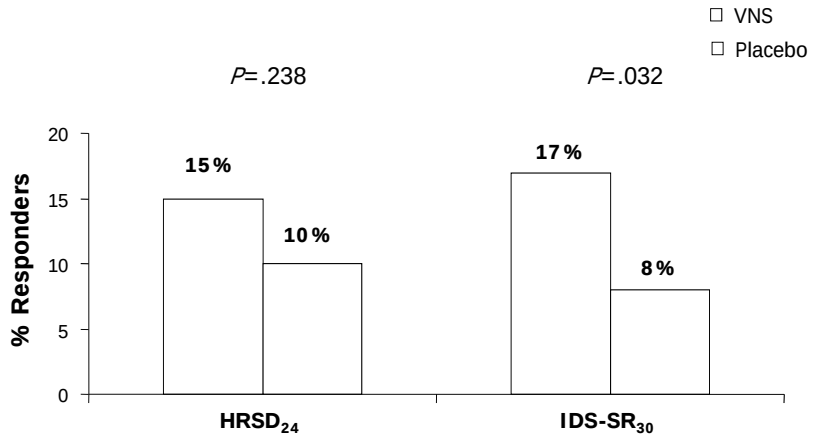
D-02 Study Design

10 weeks of VNS (8 weeks fixed dose stimulation)



D-02 Acute Response Rates

(n=222 – Evaluable Group)



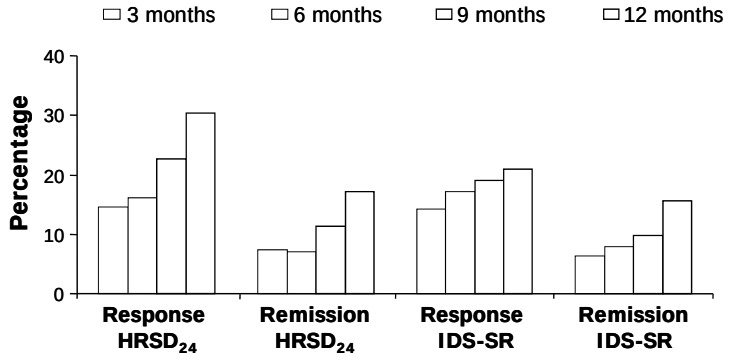
D-02 Treatment-Emergent AEs (≥5%) Possibly Related to Implantation

Preferred Term	Total (N=235) %
Percentage of subjects with at least one adverse event	38
Device site pain	23
Device site reaction	14
Headache	8
Incision	36
Neck pain	7
Pain	7
Dysphagia	11
Nausea	9
Hypesthesia	11
Paresthesia	6
Cough increased	6
Dyspnea	9
Pharyngitis	13
Voice alteration	33
Incision site reaction	29

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

D-02 Long-Term Patient Outcomes

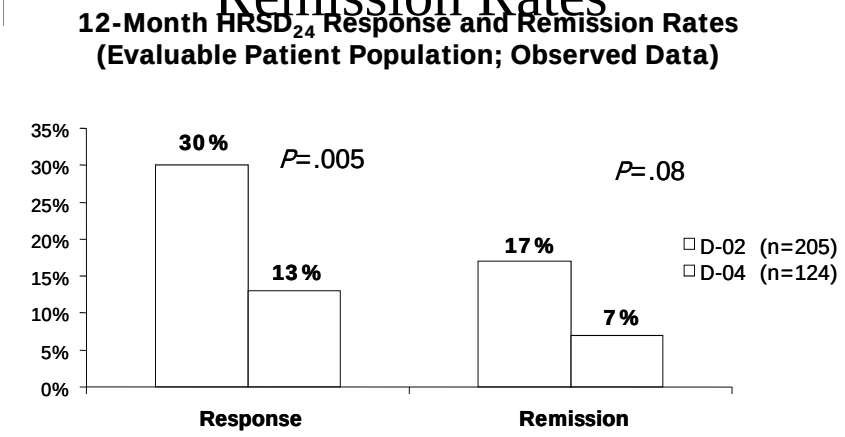
IDS-SR and $HRSD_{24}$ Response and Remission (Evaluable Patients)



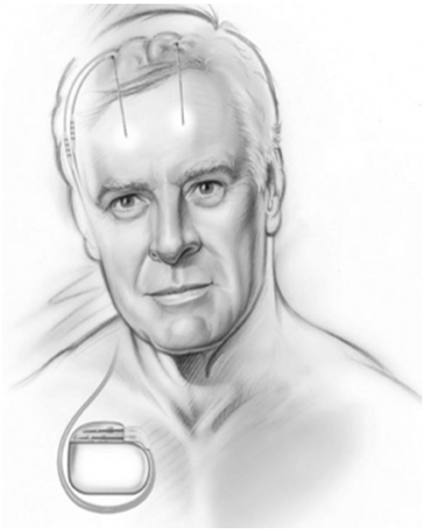
D-04: An Observational Study of Long-Term Outcomes in Treatment-Resistant Depression

- 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



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

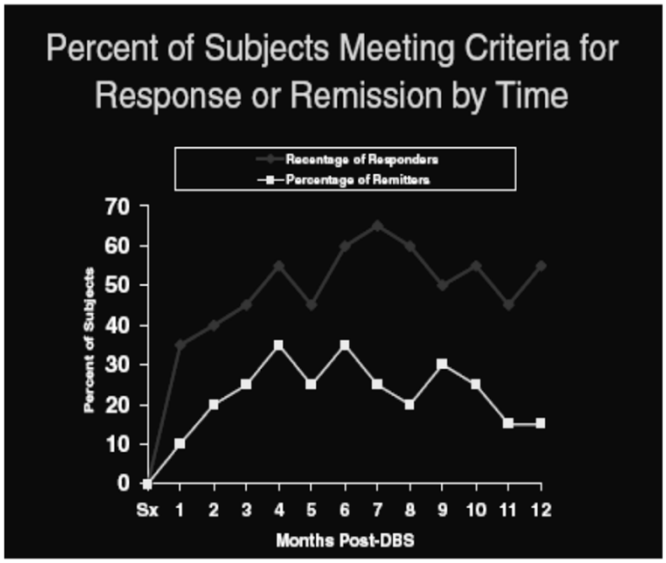


Figure 2. Patients meeting response or remission criteria after DBS. The proportion of patients responding or reaching remission increased over time to plateau from 6 to 12 months. DBS, deep brain stimulation.

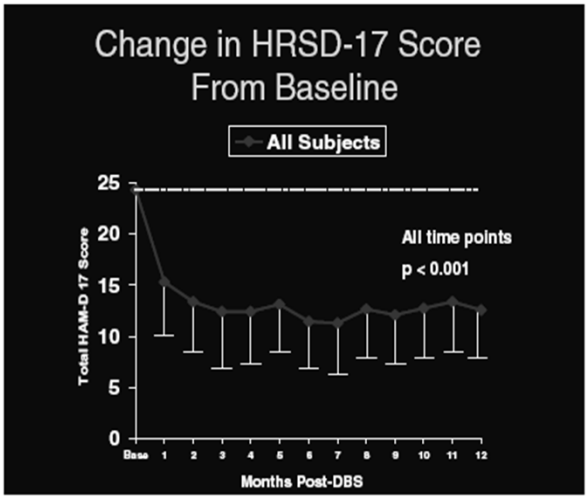
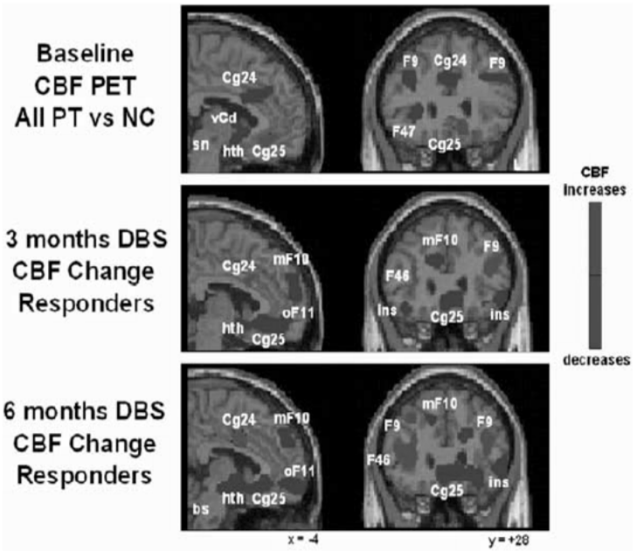


Figure 1. Mean HRSD-17 score for 20 patients with TRD receiving SGC DBS at baseline and at subsequent visits over a 12-month period. The values at all time points from 1 to 12 months are significantly different compared with baseline $p < .001$. Error bars indicate standard deviation. DBS, deep brain stimulation; HRSD-17, 17-item Hamilton Rating Scale for Depression; SGC, subcallosal cingulate gyrus; TRD, treatment-resistant depression.

Increased Blood Flow in the Subgenual Anterior Cingulate (Cg25) In Major Depression—Changes with Deep Brain Stimulation



Mayberg, 2005

Figure 2. PET Scans

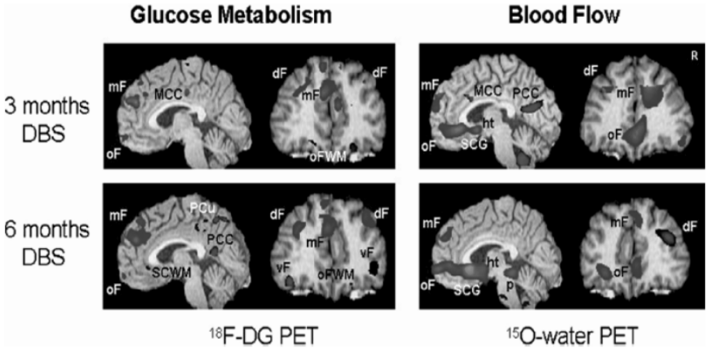
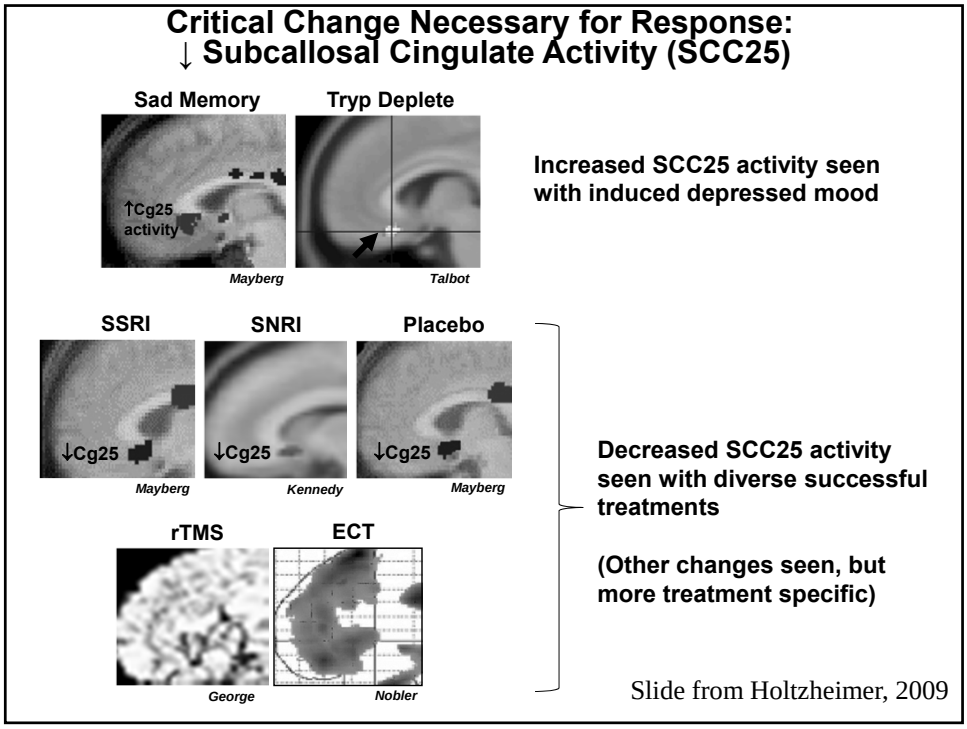
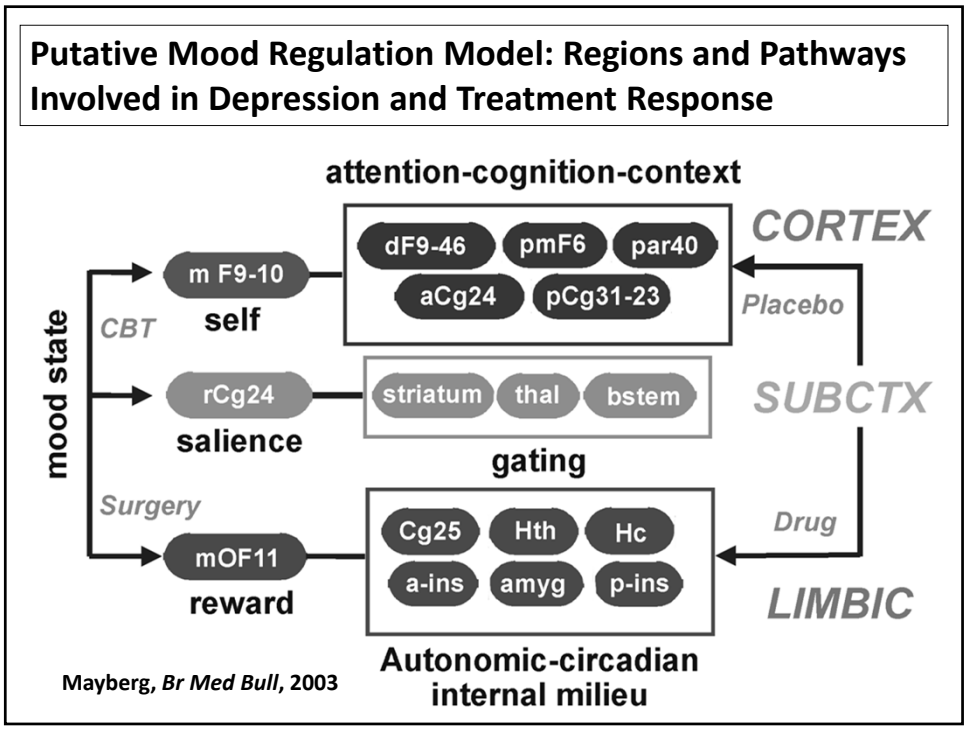


Figure 3. Changes in regional activity in TRD patients treated with chronic SCG DBS. Changes relative to baseline in DBS responders studied at 3 and 6 months of treatment using ^{18}F-fluoro-deoxyglucose PET (FDG, n=8) or ^{15}0 water blood flow PET (n=3). Increases in activity shown in red; decreases in blue; significance threshold $p<.005$. Note similar pattern of relative glucose metabolism and blood flow changes in orbital frontal (oF), medial frontal (mF), dorsolateral prefrontal (dF) and posterior cingulate (PCC) with both tracers. Discordance is seen in the subcallosal cingulate gyrus target region (SCG) with focal glucose metabolic increases restricted to the adjacent white matter (SCWM) in the FDG scans and more widespread SCG decreases in the blood flow scans. Abbreviations: 18FDG, 18F-fluoro-deoxyglucose; DBS, deep brain stimulation; dF, dorsal frontal; ht, hypothalamus; mF, medial frontal; MCC, mid cingulate cortex; oF, orbital frontal; ofWM, orbital frontal white matter; p, pons; PCu, precuneus; PCC, posterior cingulate cortex; PET, positron emission tomography; SCG, subcallosal cingulate gyrus; SCWM, subcallosal cingulate white matter; vF, ventral frontal.


Critical Change Necessary for Response:
↓ Subcallosal Cingulate Activity (SCC25)
Sad Memory
Tryp Deplete
↑Cg25 activity
Mayberg
Talbot
Increased SCC25 activity seen with induced depressed mood
SSRI
SNRI
Placebo
↓Cg25
↓Cg25
↓Cg25
Mayberg
Kennedy
Mayberg
rTMS
ECT
George
Nobler
Decreased SCC25 activity seen with diverse successful treatments
(Other changes seen, but more treatment specific)
Slide from Holtzheimer, 2009


Putative Mood Regulation Model: Regions and Pathways Involved in Depression and Treatment Response
attention-cognition-context
CORTEX
dF9-46
pmF6
par40
aCg24
pCg31-23
m F9-10
self
CBT
Placebo
mood state
rCg24
salience
striatum
thal
bstem
gating
SUBCTX
Surgery
Drug
mOF11
reward
Cg25
Hth
Hc
a-ins
amyg
p-ins
LIMBIC
Autonomic-circadian internal milieu
Mayberg, Br Med Bull, 2003

Washington State Health Care Authority
Health Technology Assessment

DRAFT Key Questions and Background

Nonpharmacologic Treatments for Treatment-Resistant Depression

Public comments on the draft key question will be accepted until 5 pm, October 3, 2013.

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.