### Order of Scheduled Presentations

**TOPIC:** Treatment-resistant Depression

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<th>Name</th>
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<tr>
<td>1.</td>
<td>John Neumaier, MD, PhD</td>
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<td>2.</td>
<td>Anna Borisovskaya, MD</td>
<td>No slides.</td>
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<td>3.</td>
<td>Farrokh Farrokhi, MD</td>
<td>Vice President, WA State Association of Neurological Surgeons</td>
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<td>4.</td>
<td>Mercy Yule, EAMP</td>
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Disclosure

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If yes, list name of organizations that relationship(s) are with and for #6, describe other relationship:

____________________________________________________________________________________

____________________________________________________________________________________

If yes to #7, provide name and funding Sources: I am a faculty member of the University of Washington Department of Psychiatry but I am presenting my own professional opinions and am not representing the department, hospital or University formally but am stating this for clarity sake.

If you believe that you do not have a conflict but are concerned that it may appear that you do, you may attach additional sheets explaining why you believe that you should not be excluded.

I certify that I have read and understand this Conflict of Interest Form and that the information I have provided is true, complete, and correct as of this date.

X  John F Neumaier, MD, PhD

Signature  Date  Print Name

Feb 20, 2014

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA  98504-2712
360-725-5126
Disclosure

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[Handwritten text: VAMC - I work here. VA has no stakeholder interest in the products or treatments I will be discussing.]

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[Handwritten signature] 02/21/14 [Handwritten print name]

For questions contact: Christine Masters  
Health Technology Assessment  
PO Box 42712  
Olympia, WA 98504-2712  
360-725-5129
Disclosure

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X __________________________ 2/27/14 __________________________
Signature Date Print Name

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126
Comments on

Deep Brain Stimulation for Treatment Resistant Depression

Farrokh Farrokhi, MD
Neurosurgery - Virginia Mason
Vice President - Washington State Association of Neurological Surgeons
March 21, 2014

Request on behalf of WSANS/AANS/CNS to:

Defer decision of DBS for TRD

Due to insufficient evidenced

- HTA Analysis:
  - "The evidence was insufficient to allow conclusions."
  - "A single uncontrolled study evaluated certain response predictors."
  - "No controlled studies have been published."
  - "DBS can result in serious complications."
  - "narrative review article provided an estimate that hemorrhage can occur in up to 10% of patients (regardless of indication)."
Toronto: Continued Proof-of-Principle Testing
Unblinded, safety and efficacy testing of chronic stimulation

- 20 patients: 1 Year Follow-up
- All time points
  - Resp=60%; Resp=55%
  - months after implant
  - Total HAM-D 17 Score
  - p < 0.001

- Long Term fl/u: 3-6 yrs, n=14
- Resp 62.5% 46.2% 75% 64% 36% 58% 42%
- Rem 18.8% 15.4% 50% 42% 36% 65% 58%
- avg=42 mo

Emory Studies: Replication, Extension

- Entry Criteria
  - 10UP/7BP2; 10W/7M; age 42±9, MDE 5.3±4y
  - Meds stable, 1 mo placebo, 6 mo open DBS
  - First patient Jan 12, 2007

- Funding: Dana, Stanley, Woodruff Found’n, Emory Hosp
- Devices donated by St. Jude Medical, IDE: G060028/S002

- • time course, remission rate, similar to Toronto
- • modest sham effect; carryover from OR?
- • Continued improvement over time
- • if Remitter, no spont relapses, more resilient?

Spain n=8 62% 1 yr
SJM pilot n=21 48% 6 mo (3 centers)
- case reports (Argentina, GR, Calgary)

Funding: Dana, Stanley, Woodruff Found’n, Emory Hosp
Devices donated by St. Jude Medical, IDE: G060028/S002
One Source of Response Variability
surgical precision

Location of Active Contacts
Standardized to AC-PC mean MNI space

Voltage Field Modeling (TAM)

6m R
N=6

6m NR
N=9

Overlap

Simple Localization is not adequate even when done ideally
Need individual tract maps to ensure full coverage of critical
White matter bundles for each patient.
Disclosure

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[Signature]
2/16/2014

MERCY YULE, CAMP

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126
TO: Christine Masters

FROM: Mercy Yule, EAMP

DATE: 28 Feb 2014

RE: Participant disclosure for presentation March 21, 2014

I believe that I do not have any conflict of interest. However, I currently am a member of, and do committee work with the Washington East Asian Medicine Association, a professional group of which I was formerly president, to promote understanding of and access to acupuncture and East Asian Medicine services.

Mercy Yule, EAMP

28 Feb 2014
ACUPUNCTURE FOR TREATMENT OF RESISTANT MAJOR DEPRESSIVE DISORDER

Mercy Yule, EAMP

Introduction

- Acupuncture has a record of safety with few serious adverse events.
- Better research studies on acupuncture for many conditions are becoming available.
- Although more research is needed specifically on the population with conditions that resist current treatments, research shows that acupuncture is safe and effective for treatment of Major Depressive Disorder.
Studies: Acupuncture for MDD


Whole body acupuncture for major depressive disorder

- Single-blind placebo controlled study of 70 inpatients with major depressive disorder divided into three groups:
- Specific standardized acupuncture points
- Non-specific acupuncture points
- Pharmacological management
- Treatments were given for a period of 4 weeks
- Patients were evaluated 2 times a week for 8 weeks by judges who were blinded to the treatment.
Whole body acupuncture for major depressive disorder

GAS

weeks

mianserin  verum  placebo

GAS ratings (global assessment) over time (the better the score, the better the psychopathology).

Whole body acupuncture for major depressive disorder

Bf-S

weeks

mianserin  verum  placebo

Bf-S self ratings (depressive mood) over time (the lower the score, the better the psychopathology).
**Whole body acupuncture for major depressive disorder**

**mean diazepam medication**

![Graph showing mean diazepam medication over 8 weeks with different treatments: mianserin, verum, placebo.]

**Whole body acupuncture for major depressive disorder**

**CGI item 2**

![Graph showing CGI item 2 ratings over 8 weeks with different treatments: mianserin, verum, placebo.]

CGI ratings (item 2 = improvement) over time (the lower the score, the better the psychopathology).
Conclusion: “Acupuncture did improve the course of depression more than pharmacological treatment...”
Acupuncture combined with paroxetine for MDD

- An RCT with 160 patients diagnosed with MDD assigned to one of three groups:
  - Paroxetine alone
  - Paroxetine combined with acupuncture
  - Paroxetine combined with electroacupuncture
- This was a 6 week trial with a 4 week follow up, using the Hamilton Depression Rating Scale (HAMD-17), the Self-rating Depression Scale (SDS), and clinical evaluation (CGI-S).
Acupuncture combined with paroxetine for MDD

- Conclusion “Collectively, as most antidepressant agents have broad side effects, acupuncture in manual and electrical stimulation modes provides a safe and effective treatment in augmenting the antidepressant efficacy…”
Many studies indicate that inflammation plays an important role in the etiology of Major Depressive Disorder.

An imbalance of Th1 and Th2 has been reported in severe psychiatric disorders.

Acupuncture has been used to treat severe psychiatric disorders.

Acupuncture has been shown to affect serotonin levels. There may be other mechanisms at work.

95 patients with MDD were treated for 6 weeks divided into three groups:

- Fluoxetine
- Electroacupuncture (EA)
- Placebo

Evaluated with Hamilton Depression Rating Scale and Clinical Global Impression Scale

Serum cytokine levels were measured by ELISA
Conclusion: “The antidepressant treatment with fluoxetine showed an anti-inflammatory effect by reducing pro-inflammatory cytokines, while EA treatment not only reduced pro-inflammatory cytokines but also modified Th2 cytokine synthesis and restored the balance in the Th1/Th2 ratio.”

**Neural imaging of acupuncture**: Huang et al, 2012
Meta-analysis of 207 studies on acupuncture for depression; 133 were on MDD, 15 on PSD (Post-stroke depression). 20 of the RCT’s on MDD were considered high quality according to JADAD scale.
Systematic review: Acupuncture for depressive disorders

Conclusion: “The efficacy of acupuncture as a monotherapy was comparable to antidepressants alone in improving clinical response and alleviating symptom severity of MDD…”

Conclusion

- Although the nature of the present review is to consider specific non-pharmacological therapies for treatment resistant Major Depressive Disorder, acupuncture might also be considered. Acupuncture can treat MDD when used alone, and can reduce the medication burden when used in conjunction with pharmaceutical therapy.
Nonpharmacological Treatments for Treatment-resistant Depression

Clinical Expert

David H. Avery, M.D.
Professor Emeritus, University of Washington School of Medicine
Medical Staff, Swedish Medical Center
Disclosure
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Cerave Neurotech Inc. - Data & Safety Monitoring Board - $1,500 per year - This company makes TMS machines. Clinically I administer.

Elecroconvulsive Therapy

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[Signature] 2/23/14

[Name]

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5128 (Fax: 360-586-8827)
CURRICULUM VITAE
DAVID HARTFORD AVERY

PERSONAL DATA:
Date of Birth: May 31, 1946
Birthplace: Gary, Indiana

CURRENT ADDRESS:
Psychiatric Medicine Associates
1505 Westlake Ave N. Suite 920
Seattle, WA 98109

EDUCATION:
Wabash College, Crawfordsville, Indiana
  B.A., Religion, Chemistry, May 1968
Washington University School of Medicine, St. Louis, Missouri
  M.D., Medicine, May 1972

POST GRADUATE TRAINING:
7/1972-6/1973 Internship (Internal Medicine), University of Iowa Hospital, Iowa City, Iowa
7/1973-6/1976 Residency in Psychiatry, University of Iowa Hospital, Iowa City, Iowa
8/1976-7/1977 Fellowship in Psychopharmacology with Dr. Leo Hollister at the Palo Alto VA Hospital
8/1977-12/1977 Post-Doctoral Scholar in Psychiatry, Stanford University School of Medicine
1/1978-1/1980 NIMH Post-Doctoral Fellow with Dr. Ole Rafaelsen at the Psychochemistry Institute, University of Copenhagen, Copenhagen, Denmark

FACULTY POSITIONS HELD:
4/1980-6/1984 Assistant Professor of Psychiatry, University of Washington School of Medicine, Seattle, WA
7/1984-6/1999 Associate Professor, University of Washington School of Medicine, Seattle, WA
7/1999-9/2012 Professor, University of Washington School of Medicine
10/2012- Present Professor Emeritus, University of Washington School of Medicine
HOSPITAL POSITIONS HELD:

4/1980-present Attending Psychiatrist, Harborview Medical Center
7/1982-6/1987 Director of Inpatient Psychiatry, Harborview Medical Center
7/1993-2/2011 Director of Inpatient Psychiatry, Harborview Medical Center

CURRENT AFFILIATION:

Psychiatric Medicine Associates
Medical Staff, Swedish Medical Center

HONORS:

Phi Beta Kappa; Summa Cum Laude, American Psychiatric Association Distinguished Fellow

BOARD CERTIFICATIONS:

National Board of Medical Examiners, Parts I, II, III, 1973
American Board of Psychiatry and Neurology, January, 1981

CURRENT LICENSE:

State of Washington - #025209 MD00018099

PROFESSIONAL ORGANIZATIONS:

1977-1985 Collegium Internationale Neuro-Psychopharmacologicum
1981-1987 American Psychopathological Association
1981-2011 Society of Biological Psychiatry
  George M. Thompson Award Committee Member, 1995-97
1983-present American Psychiatric Association
1984-2001 West Coast College of Biological Psychiatry, (President, 1992-1993)
1989-1995 Sleep Research Society
1989-1999 Society for Light Treatment and Biological Rhythms,
  (Chair, DSM-IV Committee, 1990; Chair, Publications Committee,
   1996-98.)
  (Chair, Federal Industrial Relations Committee, 1992-98);
  Board Member, 1995-1998
1997-present International Society for Transcranial Simulation (ISTS), now renamed The
  International Society for ECT and Neurostimulation.
TEACHING RESPONSIBILITIES:

Course 665 (Third Year Medical Student Psychiatry Clinical Clerkship) over the past 30 years. Supervision of second year medical students in Human Biology 560 (1981-1985). Lectures to Residents in their R-1, R-2, and R-3 years. I have been in charge of the Mood Disorders Module of the R-2 Residents since 2005. Mentor for 8 medical students in their research projects. Mentor of two Ph.D. graduate students in physiological psychology. Mentor for three Senior Fellows for training in transcranial magnetic stimulation.

EDITORIAL RESPONSIBILITIES:

Editorial Advisory Board for Clinical Advances in the Treatment of Psychiatric Disorders.

JOURNAL REFEREE:

Acta Psychiatric Scandinavica
American Journal of Physiology
American Journal of Psychiatry
Archives of General Psychiatry
Biological Psychiatry
Bipolar Disorders
Chronobiology International
Comprehensive Psychiatry
Convulsive Therapy
General Hospital Psychiatry
International Journal of Neuropsychopharmacology
Journal of Alternative and Complementary Medicine
Journal of Abnormal Psychology
Journal of Affective Disorders
Journal of Clinical Psychiatry
Journal of ECT
Journal of Nervous and Mental Disease
Journal of Psychiatric Research
Journal of Psychosomatic Research
Journal of Sleep Research
Neuropsychopharmacology
Progress in Neuro-Psychopharmacology and Biological Psychiatry
Psychiatry Research
Psychosomatic Medicine
Sleep
Women’s Health in Primary Care
SPECIAL NATIONAL RESPONSIBILITIES:

Chairperson for a National Institute of Mental Health Special Emphasis Panel (ZMH1 CRB-U (04). 2003
Ad Hoc reviewer for the NIMH Board of Scientific Counselors.
Ad Hoc reviewer for NIMH study sections.
Ad Hoc reviewer for VA study sections.
Ad Hoc reviewer for the British Health Care Research Foundation
Ad Hoc reviewer for the Canadian Institutes of Health Research
Ad Hoc reviewer for American Institute of Biological Sciences
Visiting Professor at Tanta University, Tanta, Egypt, February, 2004.
Planning Committee Member for a VA Cooperative Study (#556) “The Effectiveness of TMS in Depressed VA Patients.” 2005-
Visiting Professor at Hebei Medical University, Shijiazhuang, China, October, 2008.
TMS Course Faculty and Organizing Committee for the Certificate Course on Transcranial Magnetic Stimulation (TMS) at the Association for Convulsive Therapy Meeting, May, 2009.

SPECIAL LOCAL RESPONSIBILITIES:

1982-1984 Human Subjects Committee
1984-1988 Residency Site Coordinator
1984-2005 Spiritual Care Board (Harborview Medical Center)
1985-1988 Graduate Education Steering Committee (Department of Psychiatry and Behavioral Sciences)
1988-1989 Chair, Pastoral Care Board (Harborview Medical Center)
1992-2000 Scientific Advisory Committee for the Clinical Research Center, (University of Washington School of Medicine)

GRANTS:

Principal Investigator for the following grants:
Graduate School Research Fund Grant "REM Latency and Thermoregulation in Depression." 1982-1983 $4,000.
Research Scientist Development Award (MHK 1 KO1 MH00493-01A2) "EEG Sleep and Temperature Rhythm in Primary Depression." September 1, 1987 to August 31, 1992, $414,062.


NIMH RO1 Grant, "Dawn Simulation and Bright Light Treatment of SAD." August 1, 1995 to July 31, 1999, $427,037.

Royalty Research Fund Grant "Repetitive Transcranial Magnetic Stimulation Treatment of Major Depression", 7/15/97-7/14/98, $24,500.

Grant from Philips DAP Suncare "Bright Light Therapy of Subsyndromal Seasonal Affective Disorder", 12/15/98-6/15/03, $50,000

Associate Investigator with School of Nursing, NIH Grant, National Center for Research Resources Shared Instrumentation Grant. "Physiological Data Systems." March 1, 1991 to February 28, 1993, $359,000.

Co-Principal Investigator with School of Nursing, NIH/NINR RO1 Grant, “Nurse Administered Therapy for Agitation in Elders” July 1, 1996 to June 30, 1999, $807,415.

Principal Investigator, NIMH RO1 MH 62154 "TMS Treatment of Major Depression" 8/15/00- 7/31/04 - $1,114,036

Principal Investigator of industry funded study of transcranial magnetic stimulation by Neuronetics, Inc. “A Randomized, Parallel-Group, Sham-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of the Neuronetics MODEL 2100 CRS Repetitive Transcranial Magnetic Stimulation (rTMS) System in Patients with Major Depression” 3/25/04-09/14/05, up to $180,000.

Principal Investigator, NIMH RO1 MH 69929 "Optimization of TMS for Depression" 9/15/04-5/31/10 - $1,364,400

Principal Investigator, NIAMS R21 AR053963 "Transcranial Magnetic Stimulation in the Treatment of Chronic Widespread Pain" 9/01/07- 8/31/10 - $368,940.
BIBLIOGRAPHY:

Original Investigations:

Original Investigations: (continued)


Original Investigations: (continued)


CHAPTERS:
ARTICLES IN NON-REFEREED JOURNALS:


Abstracts (First-Author)

Regional Meetings:


"TSH and Temperature Rhythms in Winter Depression" West Coast College of Biological Psychiatry, San Francisco, April 7, 1990.

"Is the Temperature Setpoint Elevated in Depression?" West Coast College of Biological Psychiatry, San Diego, April 6, 1991.

"Dawn Simulation Treatment of Winter Depression: A Second Controlled Study" Meeting of the West Coast College of Biological Psychiatry, Santa Monica, April 11, 1992.

"Is the Low Temperature Trough Duration Increased During a Constant Routine in Winter Depression?" West Coast College of Biological Psychiatry, Seattle, April 17, 1993.

“Is PSI E-M Increased in Winter Depression?” West Coast College of Biological Psychiatry, Seattle April 17, 1993.


"Dawn Simulation and Bright Light in the Treatment of Winter Depression" West Coast College of Biological Psychiatry, Long Beach, April 21, 2001.

"Transcranial Magnetic Stimulation Treatment of Major Depression" West Coast College of Biological Psychiatry, Long Beach, April 21, 2001.


“Seasonal Affective Disorder” Psychiatry Update, Seattle, February 3, 2005.


“Insomnia” Valley Hospital and Medical Center, Spokane Valley, Washington, March 20, 2007.

“Coping with Jet Lag” The Gates Foundation, Seattle, WA 5/21/07

“Transcranial Magnetic Stimulation in Psychiatry” Northwest Hospital, Seattle, WA 6/27/07


National

"A Three Year Follow-Up Study of Depression Treated with ECT or Antidepressant Therapy, society of Biological Psychiatry, San Francisco, June, 1976.


"REM Sleep and Nocturnal Temperature in Depression" American College of Neuropsychopharmacology, San Juan, Puerto Rico, December, 1983.

"Dexamethasone Suppression Test in Anxiety Disorders and Depression" Psychiatry Research Society, Park City, Utah March 9, 1984.


"Phase Typing Seasonal Affective Disorder using a Constant Routine" Society for Light Treatment and Biological Rhythms, Washington DC, June 22, 1989.


"Rectal Temperature and TSH During a Constant Routine in Winter Depression" Association of Professional Sleep Societies, Minneapolis, June 1990


"Difficulty Awakening as a Symptom of Winter Depression" Meeting of the Society of Light Treatment and Biological Rhythms, Bethesda, MD, June 23, 1994.

"Temperature Rhythms and Sleep in a 48-Hour Cyclothymic Patient" Meeting of the Society for Light Therapy and Biological Rhythms, Bethesda, MD, June 3, 1996.


"Dawn Simulation and Bright Light Treatment of SAD" Meeting of the Society of Light Treatment and Biological Rhythms, Chicago, May 8, 2000.

"Dawn Simulation and Bright Light Treatment of SAD" Meeting of the Society of Biological Psychiatry, New Orleans, May 5, 2001

"Transcranial Magnetic Stimulation in the Treatment of Depression" NCDEU Meeting, Phoenix, AZ, May 29, 2001
“Repetitive transcranial magnetic stimulation (rTMS) is clinically effective in treatment-resistant major depression.” Society of Biological Psychiatry, New York, May 1, 2004.

“The Efficacy of Transcranial Magnetic Stimulation in Major Depression” NCDEU Meeting, Phoenix, AZ, June 2, 2004

International:
Suicide, Attempted Suicide, and Relapse Rates in Depression Following ECT and Antidepressant Therapy" VI World Congress of Psychiatry, Honolulu, August, 1977.


"Sleep EEG and Body Temperature in Depression" 4th World Congress of Biological Psychiatry, Philadelphia September 11, 1985.

"Temperature Rhythm Phase-Typing of Seasonal Affective disorder and Response to AM and PM Bright Light” 5th International Congress of Sleep Research, Copenhagen, Denmark, June, 1987.


"Dawn Simulation in the Treatment of Abstinent Alcoholics"  Meeting of the Society for Light Treatment and Biological Rhythms, Frankfurt, Germany, June 10, 1995.

"rTMS Treatment of Depression: Preliminary Data"  Conference on Transcranial Magnetic Stimulation (TMS), Interlaken, Switzerland, August 12, 1997.


“Transcranial Magnetic Stimulation in the Treatment of Medication-Resistant Depression and Chronic Widespread Pain.”  Hebei Medical University, Shijiazhuang, China, October 11, 2008.

“Seasonal and Circadian Aspects of Mood Disorders and the Use of Light Therapy”  Hebei Medical University, Shijiazhuang, China, October 11, 2008.


Selected abstracts of collaborators who were first authors:


Helleckson CJ, Avery D, Stolz SE, Pascualy RA: "Does Weight Gain in SAD Predispose to Sleep Apnea Syndrome?" Society of Light Treatment and Biological Rhythms, Bethesda, May, 1992.


Eder DN and Avery DH. "Sleep architecture in symptomatic SAD and changes following dawn simulation: A naturalistic study." Poster presentation at the Society for Light Therapy and Biological Rhythms annual meeting, La Jolla, June 1993.

Eder DN and Avery DH: "Being cool: Skin temperature changes are dependent on delta-EEG intensity." Presented at the 12th Congress of the European Sleep Research Society, Florence, May 1994 and at the 9th annual meeting of the Association of Professional Sleep Societies, Boston, June 1994.


Eder DN and Avery DH: "Stuffing the physiological pillow? A relationship between the rate of decline in core body temperature and delta-EEG during sleep." J. Sleep Res. 5(suppl. 1):55, 1996.


**Invited Presentations:**

"ECT and Antidepressants in the Treatment of Depression". Psychochemistry Institute, University of Copenhagen, Copenhagen, Denmark, April, 1978.


"ECT and Antidepressants in the Treatment of Depression" Fredericksberg Hospital, Fredericksberg, Denmark, September, 1978.

"Temperature Rhythms and REM Sleep in Depression", Psychochemistry Institute, University of Copenhagen, Copenhagen, Denmark, January, 1980.

"Temperature Rhythms and REM Sleep in Depression" Max Planck Institute, Munich, West Germany, March, 1980.

"ECT and Antidepressants in the Treatment of Depression" University of Munich Department of Psychiatry, Munich, West Germany. March, 1980.

"REM Sleep and Circadian Rhythms in Affective Disorder" University of Iowa, Grand Rounds, February, 1982.


"Light Boxes, Light Visors, Dawn Simulators, and SSRIs: Which is the Best Approach to Treat Winter SAD?" Meeting of the Society for Light Treatment and Biological Rhythms, June 24, 1994.


"Recent Advances in the Treatment of Seasonal Affective Disorder" Psychochemistry Institute, University of Depression" University of Iowa, September 23, 1996.

"Recent Advances in the Treatment of Seasonal Affective Disorder" Grand Rounds, University of Iowa, September 24, 1996.


"Transcranial Magnetic Stimulation Treatment of Depression" Psychochemistry Institute, University of Copenhagen, Copenhagen, Denmark, August 18, 1997.

"Transcranial Magnetic Stimulation Treatment of Depression" Gentofte University, Gentofte, Denmark, April 1, 1998.

"Transcranial Magnetic Stimulation Treatment of Depression" Grand Rounds, Oregon Health Sciences University, Portland, September 14, 1999.


"Psychopharmacology of Aggression" Seattle Forensic Institute, Seattle October 21, 1999.

"Light Treatment of SAD and Other Psychiatric Disorders" Psychiatry Update, Seattle, Nov. 18, 1999.


"Recent Advances in Light Therapy in the Treatment of SAD and Other Disorders" Steven's Hospital, Edmonds, WA January 18, 2000
"Light therapies for winter depression and other psychiatric disorders.", Grand Rounds, Sacred Heart Medical Center, Spokane, March 14, 2000.

"Management of Treatment-Resistant Depression: New Antidepressants and New Approaches in Light Therapy" Northwest Mental Health Institute, Redmond, Oregon, June 9, 2000


"Light, Melatonin, and Sleep" Grand Rounds, Overlake Hospital, March 13, 2001.

"ECT and Transcranial Magnetic Stimulation in Treatment Resistant Depression" Nonpharmacological Approaches to Treatment Resistant Depression, April 28, 2001.


“Recent Advances in the Treatment of Seasonal Affective Disorder.” Alaska Native Hospital, Anchorage, Alaska, April 18, 2002.

“Recent Advances in the Treatment of Seasonal Affective Disorder.” Providence Hospital, Anchorage, Alaska, April 19, 2002.

“Recent Advances in the Treatment of Seasonal Affective Disorder.” Alaska Regional Hospital, Anchorage, Alaska, April 19, 2002.


“Psychopharmacologic Management of Agitation” CME presentation at Western State Hospital, Steilacoom, WA, February 6, 2003.


“Transcranial Magnetic Stimulation in the Treatment of Depression” Oringe Hospital, Vordingborg, Denmark, June, 2004


“The Use of Repetitive Transcranial Magnetic Stimulation (rTMS) and Vagus Nerve Stimulation (VNS) in Treating Depression” UCLA’s Twelfth Annual Review of Psychiatry and Psychopharmacology Update- Evidence Based Treatments” University of California, Los Angeles, Los Angeles, CA October 27, 2007.


“Transcranial Magnetic Stimulation in the Treatment of Medication-Resistant Depression and Chronic Widespread Pain.” Hebei Medical University, Shijiazhuang, China, October 11, 2008.

“Seasonal and Circadian Aspects of Mood Disorders and the Use of Light Therapy” Hebei Medical University, Shijiazhuang, China, October 11, 2008.

“Transcranial Magnetic Stimulation in the Treatment of Medication-Resistant Depression and Chronic Widespread Pain.” Beijing Medical University, Beijing, China, October 14, 2008.


Non-Pharmacologic Therapies for Treatment Resistant Depression

Charissa Fotinos, MD, MSc
Deputy Chief Medical Officer
WA State Health Care Authority

Agency Medical Director Comments

- Major depressive disorder is common
  - Annual prevalence in US adults 6.7%
  - Lifetime prevalence for US adults: 16.5%
- Diagnostic criteria unchanged in DSM-V
  - Requires the presence of 5 or more symptoms including a depressed mood or loss of pleasure for at least 2 weeks
- Usual treatment includes pharmacotherapy, psychotherapy or both
- Standard of care is to treat for 4-8 weeks and if the response is inadequate, change or add another agent

Treatment Resistant Depression (TRD)

http://www.nimh.nih.gov/statistics/1mdd_adult.shtml
Treatment Resistant Depression (TRD) Setting the Stage

Some definitions:
- No response < 25% improvement
- Partial response 26-49%
- Response >50% improvement
- Remission: rating back to the normal range of the depression scale being used

How common is TRD?
- STAR*D Trial
  - Progressive levels of treatment for patients not remitting, (Back to normal score of scale)
  - After 4 “courses” of AD therapy 67% of patients achieved remission
  - 37% did not respond

Definition of TRD
- No agreed upon definition
- Growing consensus for TRD definition = failure of >2 adequate trials of different antidepressants
  ("Adequate" lengths range from 4 - 8 weeks at max tolerable dose.)

There is no standard definition for a “clinically meaningful response”.

Treatment Modalities

- **ECT** (Electroconvulsive therapy)
- **rTMS** (repetive Transcranial Magnetic Stimulation)
- **tDCS** (transcranial Direct Current Stimulation)
- **DBS** (Deep Brain Stimulation)
AMDG Perspective

Primary Criteria Ranking

• Safety = Medium
• Efficacy = High
• Cost = Medium

FDA Status

• ECT
  – FDA approved for MDD
• rTMS
  – FDA approved for MDD
• tDCS
  – Not approved for any conditions but several devices approved as Non-significant risk devices (NSR)
• DBS
  – Not FDA approved for MDD
Current State Agency Policy

- **Uniform Medical Plan (UMP)** –
  - Regence:
    - ECT covered, does not require PA
    - rTMS, DBS considered investigational & not covered
    - No reference to tDCS
- **Medicaid** – ECT covered
- **Labor & Industries** – ECT covered
- **Department of Corrections** – No policy, patient by patient review with PA

Other Agencies & Payers

**Center for Medicare and Medicaid Services:**
No CMS National Coverage Determinations (NCDs) were identified for ECT, rTMS, tDCS, or DBS for the treatment of depression on September 17.

**Oregon Health Evidence Review Commission (HERC):**
The Oregon HERC has concluded that rTMS and ECT should be covered for patients with an episode of MDD who have failed at least 2 pharmacologic treatments. There was no information on tDCS or DBS.

**Group Health:**
ECT covered, rTMS not covered, tDCS and DBS not mentioned as options for depression
**Electroconvulsive Therapy (ECT)**

### Electroconvulsive Therapy, All Agency Summary, 2009-2012

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>4 Yr Overall Total**</th>
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<tbody>
<tr>
<td><strong>ECT Patients</strong> (any diagnosis*)</td>
<td>71</td>
<td>89</td>
<td>78</td>
<td>61</td>
<td>213</td>
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<tr>
<td><strong>ECT Procedures</strong> (treatment days)</td>
<td>568</td>
<td>655</td>
<td>665</td>
<td>533</td>
<td>2421</td>
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<tr>
<td>Average Count per Patient</td>
<td>8.0</td>
<td>7.4</td>
<td>8.5</td>
<td>8.7</td>
<td>11.4</td>
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<tr>
<td>Max Count per Patient</td>
<td>48</td>
<td>48</td>
<td>62</td>
<td>49</td>
<td>205</td>
</tr>
<tr>
<td><strong>ECT Total Paid</strong></td>
<td>$354,296</td>
<td>$355,896</td>
<td>$455,032</td>
<td>$389,658</td>
<td>$1.6M</td>
</tr>
<tr>
<td>Average Paid per Patient</td>
<td>$4,990</td>
<td>$3,999</td>
<td>$5,834</td>
<td>$6,388</td>
<td>$7,300</td>
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<td>Average Paid per Procedure</td>
<td>$624</td>
<td>$543</td>
<td>$684</td>
<td>$731</td>
<td>$642</td>
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</tbody>
</table>

**PEB/UMP and L&I** – 100% episodic and depression diagnoses

**Medicaid** – 85% episodic & depression diagnoses. Other diagnoses: schizophrenia, psychosis

---

### PEB/UMP and ECT Top Diagnosis Codes

<table>
<thead>
<tr>
<th>Diagnosis Codes</th>
<th>Patients</th>
<th>% of All ECT Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECUR DEPR PSYCH-SEVERE</td>
<td>38</td>
<td>52.8%</td>
</tr>
<tr>
<td>RECURRE DEPR PSYCHOS-UNSP</td>
<td>31</td>
<td>43.1%</td>
</tr>
<tr>
<td>EPISODIC MOOD DISORD NOS</td>
<td>12</td>
<td>16.7%</td>
</tr>
<tr>
<td>BIPOL I SINGLE MANIC NOS</td>
<td>11</td>
<td>15.3%</td>
</tr>
<tr>
<td>DEPRESSIVE DISORDER NEC</td>
<td>11</td>
<td>15.3%</td>
</tr>
<tr>
<td>DEPRESS PSYCHOSIS-UNSPEC</td>
<td>10</td>
<td>13.9%</td>
</tr>
<tr>
<td>BIPOL I CURR DEP W/O PSY</td>
<td>8</td>
<td>11.1%</td>
</tr>
<tr>
<td>BIPOLAR DISORDER NEC</td>
<td>8</td>
<td>11.1%</td>
</tr>
<tr>
<td>BIPOL I CUR DEPRES NOS</td>
<td>7</td>
<td>9.7%</td>
</tr>
<tr>
<td>DEPRESS PSYCHOSIS-SEVERE</td>
<td>7</td>
<td>9.7%</td>
</tr>
<tr>
<td>REC DEPR PSYCH-PSYCHOTIC</td>
<td>7</td>
<td>9.7%</td>
</tr>
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</table>
## Treatment Resistant Depression: State Agency Utilization

<table>
<thead>
<tr>
<th>Medicaid ECT Top Diagnosis Codes n=134</th>
<th>Unique Patients</th>
<th>% of All ECT Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurr depr psych-severe</td>
<td>97</td>
<td>72.4%</td>
</tr>
<tr>
<td>Schizoaffective dis NOS</td>
<td>77</td>
<td>57.5%</td>
</tr>
<tr>
<td>Bipol I single manic NOS</td>
<td>64</td>
<td>47.8%</td>
</tr>
<tr>
<td>Bipol I cur depress NOS</td>
<td>53</td>
<td>39.6%</td>
</tr>
<tr>
<td>Recurr depr psychos-unsp</td>
<td>44</td>
<td>32.8%</td>
</tr>
<tr>
<td>Bipol I curr dep w/o psy</td>
<td>40</td>
<td>29.9%</td>
</tr>
<tr>
<td>Rec depr psych-psychotic</td>
<td>34</td>
<td>25.4%</td>
</tr>
<tr>
<td>Episodic mood disorder NOS</td>
<td>25</td>
<td>18.7%</td>
</tr>
<tr>
<td>Depressive disorder NEC</td>
<td>21</td>
<td>15.7%</td>
</tr>
<tr>
<td>Bipolar disorder NEC</td>
<td>13</td>
<td>9.7%</td>
</tr>
<tr>
<td>Follow-up exam NOS</td>
<td>13</td>
<td>9.7%</td>
</tr>
<tr>
<td>Simpl schizophren-unspec</td>
<td>13</td>
<td>9.7%</td>
</tr>
</tbody>
</table>

## ECT Usage

### State Agency Utilization

<table>
<thead>
<tr>
<th>PEB/UMP &amp; Medicaid Procedure Counts, 2009-2012</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>4 Yr Overall Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEB/UMP Average Annual Members</td>
<td>210,501</td>
<td>213,487</td>
<td>212,596</td>
<td>212,684</td>
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</tr>
<tr>
<td>PEB Members w/Depression (Avg 9.2%)</td>
<td>19,475</td>
<td>19,922</td>
<td>19,581</td>
<td>19,425</td>
<td></td>
</tr>
<tr>
<td>PEB/UMP ECT Patients (all with depression diagnoses)</td>
<td>26</td>
<td>32</td>
<td>30</td>
<td>30</td>
<td>72</td>
</tr>
<tr>
<td>Average Treatment Count per Patient</td>
<td>15.5</td>
<td>13.7</td>
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<tr>
<td>PEB/UMP ECT Total Paid</td>
<td>$298,744</td>
<td>$288,606</td>
<td>$384,272</td>
<td>$312,751</td>
<td>$1.3M</td>
</tr>
<tr>
<td>Medicaid Fee for Service Population</td>
<td>463,966</td>
<td>474,676</td>
<td>473,356</td>
<td>477,727</td>
<td></td>
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<tr>
<td>Medicaid Pts w/Depression (Avg 11.1%)</td>
<td>54,869</td>
<td>54,787</td>
<td>51,422</td>
<td>49,507</td>
<td>-4.30%</td>
</tr>
<tr>
<td>Medicaid ECT Patients (85% depression diagnoses)</td>
<td>43</td>
<td>55</td>
<td>45</td>
<td>28</td>
<td>134</td>
</tr>
<tr>
<td>Average Treatment Count per Patient</td>
<td>3.2</td>
<td>3.3</td>
<td>2.8</td>
<td>3.5</td>
<td>4.1</td>
</tr>
<tr>
<td>Max Treatment Count per Patient</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Medicaid ECT Total Paid</td>
<td>$26,017</td>
<td>$30,959</td>
<td>$14,574</td>
<td>$14,726</td>
<td>$86,275</td>
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### ECT Payments

#### Treatment Resistant Depression: State Agency Utilization

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<tr>
<td>Average Paid per Patient</td>
<td>$11,490</td>
<td>$9,019</td>
<td>$12,809</td>
<td>$10,425</td>
<td>$17,839</td>
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<tr>
<td>Average Paid per Patient, PEB Primary</td>
<td>$16,756</td>
<td>$10,891</td>
<td>$16,508</td>
<td>$15,548</td>
<td>$23,067</td>
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<tr>
<td>Average Paid per Procedure</td>
<td>$605</td>
<td>$563</td>
<td>$324</td>
<td>$526</td>
<td>$644</td>
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<tr>
<td>Average Paid per Procedure, Non-Medicare</td>
<td>$652</td>
<td>$686</td>
<td>$496</td>
<td>$925</td>
<td>$787</td>
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### ECT Payments

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</tr>
<tr>
<td>Average Paid per Procedure</td>
<td>$739</td>
<td>$657</td>
<td>$779</td>
<td>$823</td>
<td>$748</td>
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<tr>
<td>Average Paid per Procedure, PEB Primary</td>
<td>$1,160</td>
<td>$1,122</td>
<td>$1,138</td>
<td>$1,503</td>
<td>$1,214</td>
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<td>$14,574</td>
<td>$14,726</td>
<td>$86,275</td>
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<tr>
<td>Average Paid per Procedure</td>
<td>$191</td>
<td>$170</td>
<td>$114</td>
<td>$149</td>
<td>$158</td>
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<td>Average Paid per Procedure, Non-Medicare</td>
<td>$215</td>
<td>$227</td>
<td>$231</td>
<td>$278</td>
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### Treatment Resistant Depression: State Agency Utilization

#### ECT

<table>
<thead>
<tr>
<th>Agency Allowed Patient Charges Breakdown: ECT Average Allowed $ per Patient</th>
<th>PEB/UMP Medicare</th>
<th>PEB/UMP Primary</th>
<th>Medicaid Primary</th>
<th>Medicaid Non-Medicare Primary</th>
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<tbody>
<tr>
<td>Patient Count</td>
<td>n=21</td>
<td>n=44</td>
<td>n=43</td>
<td>n=85</td>
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<tr>
<td>Treatment Count Average</td>
<td>38</td>
<td>18</td>
<td>5</td>
<td>3</td>
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<tr>
<td><strong>Cost Breakdown 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anesthesia</td>
<td>$4,063</td>
<td>$5,432</td>
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<tr>
<td>Treatment Delivery</td>
<td>$24,682</td>
<td>$15,067</td>
<td>$950</td>
<td>$335</td>
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<tr>
<td>Hospital Care</td>
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<td>$1,336</td>
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<td>$104</td>
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<tr>
<td>Imaging/Other</td>
<td>$2,574</td>
<td>$1,463</td>
<td>$175</td>
<td>$146</td>
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<tr>
<td><strong>Cost Breakdown 2</strong></td>
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<td></td>
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<tr>
<td>Facility</td>
<td>$26,668</td>
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<tr>
<td>Provider</td>
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<td>$9,349</td>
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<td>$467</td>
</tr>
<tr>
<td><strong>Total Average Allowed</strong></td>
<td>$35,479</td>
<td>$23,299</td>
<td>$1,396</td>
<td>$674</td>
</tr>
</tbody>
</table>

### Treatment Resistant Depression: State Agency Utilization

<table>
<thead>
<tr>
<th>Agency Allowed Patient Charges Breakdown: ECT Average Allowed $ per Patient</th>
<th>PEB/UMP Medicare</th>
<th>PEB/UMP Primary</th>
<th>Medicaid Primary</th>
<th>Medicaid Non-Medicare Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Count</td>
<td>n=21</td>
<td>n=44</td>
<td>n=43</td>
<td>n=85</td>
</tr>
<tr>
<td>Treatment Count Average</td>
<td>38</td>
<td>18</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td><strong>Cost Breakdown 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anesthesia</td>
<td>$4,063</td>
<td>$5,432</td>
<td>$251</td>
<td>$88</td>
</tr>
<tr>
<td>Treatment Delivery</td>
<td>$24,682</td>
<td>$15,067</td>
<td>$950</td>
<td>$335</td>
</tr>
<tr>
<td>Hospital Care</td>
<td>$4,160</td>
<td>$1,336</td>
<td>$21</td>
<td>$104</td>
</tr>
<tr>
<td>Imaging/Other</td>
<td>$2,574</td>
<td>$1,463</td>
<td>$175</td>
<td>$146</td>
</tr>
<tr>
<td><strong>Cost Breakdown 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facility</td>
<td>$26,668</td>
<td>$13,949</td>
<td>$842</td>
<td>$207</td>
</tr>
<tr>
<td>Provider</td>
<td>$8,810</td>
<td>$9,349</td>
<td>$554</td>
<td>$467</td>
</tr>
<tr>
<td><strong>Total Average Allowed</strong></td>
<td>$35,479</td>
<td>$23,299</td>
<td>$1,396</td>
<td>$674</td>
</tr>
</tbody>
</table>
Evidence Summary: ECT

Safety:
- Low quality evidence: transient cognitive decline in some patients with autobiographic loss persisting for several months
- Insufficient data to interpret withdrawal due to lack of benefit

Efficacy:
- Low quality evidence: ECT improves symptom scores by 20%
- Moderate quality evidence: high dose and bilateral stimulation have higher effect sizes
- Insufficient evidence re: benefit in maintenance, QoL impacts, optimum treatment schedules, (freq/wk), or benefits in subpopulations

Cost: Reported both as cost saving and more expensive vs. rTMS
Evidence Summary: rTMS

Safety:
- Compared to sham, low quality evidence of more local side effects
- Compared to ECT, low quality evidence suggests no difference in cognitive effects, insufficient evidence to assess withdrawal rates due to lack of efficacy

Efficacy:
- Compared to sham: moderate quality evidence demonstrates reduction in severity, improved response and remission rates, low quality evidence, suggests the effects are short lived 2-3 weeks
- Compared to ECT*: low quality studies demonstrate mixed results on which is more effective, inconsistent impacts on QoL and function. Optimal treatment regimens or differences among subpopulations were not identified.

Cost: Low quality economic studies - mixed results, (rTMS better than drugs, ECT at times), unable to draw any conclusions

Evidence Summary: tDCS

Safety:
- Increased itching in 1 SR, no serious events, unclear effect on treatment induced mania, withdrawal rates similar to sham rates

Efficacy:
- tDCS vs. sham: Low quality studies with mixed results, 2 MA & 1 small RCT suggest improved MADRS scores
- tDCS +sertraline vs. sham and placebo: low quality studies suggest improved depression scores
- Insufficient evidence for durability, utility in maintenance, effects on QoL or the best way to use technology. There is insufficient evidence to evaluate differences across subpopulations.

Cost: No information reported
Evidence Summary: DBS

Safety:
- Serious device related events are possible, side effects reported include bleeding, infection, lead fracture and erosion, no apparent changes in cognitive function, overall insufficient evidence to state harms with certainty

Efficacy:
- Insufficient evidence from small, poor to very poor quality studies with indeterminate effects on depression relief, durability of benefit or changes in QoL/function
- Unable to draw conclusions about treatment parameters or subpopulations

Cost: No information available

State Agency Recommendations:
- **ECT:** Cover with conditions
  Severe persistent depression w or w/o psychotic features after failure of at least 2 adequate antidepressant trials w or w/o augmentation
- **rTMS:** Cover with conditions
  Severe persistent depression w or w/o psychotic features after failure of at least 2 adequate antidepressant trials with or w/o augmentation. While the available evidence does not support its superiority over ECT, its safety profile is high and for severe refractory depression it provides an alternative treatment method.
- **tDCS, DBS:** Do not cover
Questions?

More Information:
http://www.hca.wa.gov/hta/Pages/trd.aspx

Contact: shtap@hca.wa.gov
Nonpharmacologic Treatments for Treatment-Resistant Depression

Teresa L. Rogstad, MPH, Project Leader, Hayes, Inc.
March 21, 2014

Abbreviations
- AD, antidepressant (medication)
- AHRQ, Agency for Healthcare Research and Quality
- DBS, deep brain stimulation
- DLPFC, dorsolateral prefrontal cortex
- ECT, electroconvulsive therapy
- EE, economic evaluation
- HAM-D, Hamilton Depression Rating Scale
- MA, meta-analysis
- MADRS, Montgomery-Åsberg Depression Rating Scale
- MDD, major depressive disorder
- OR, odds ratio
- pt, patient
- QOL, quality of life
- RR, relative risk
- rTMS, repetitive transcranial magnetic stimulation
- SR, systematic review
- tDCS, transcranial direct current stimulation
- TRD, treatment-resistant depression
- tx, treatment or therapy
- WMD, weighted mean difference
Background

- MDD, most recent statistics, U.S. adults
  - 7% annual prevalence
  - 16.6% lifetime prevalence
- MDD and bipolar disorder = mood disorders
  - No change in MDD criteria, DSM-V vs DSM-IV
- Psychotherapy, pharmacotherapy, or both
- If inadequate response after 4–8 wks on AD
  - Switch, or
  - Augmentation
- Treatment phases: Acute, continuation, maintenance

Background: STAR*D (Sequenced Treatment Alternatives to Relieve Depression) Trial
(Rush et al., 2006; Gaynes et al., 2008)

- Remission at each step
  - Step 1 (1st AD)
  - Step 2 (1 AD Failure)
  - Step 3 (2* tx failures)
  - Step 4 (3* tx failures)

* At Step 2, 4% patients underwent psychotherapy rather than new AD
Background: TRD

- Severe MDD refractory to multiple therapies: 4M Americans
- No established definition of TRD
  - 2 systematic reviews (Berlim and Turecki, 2007; Gaynes et al., 2011 [AHRQ]):
    - Growing "consensus" that TRD = failure of ≥2 adequate trials of different ADs
    - No explicit evidence-based rationale stated in literature
    - STAR*D trial suggests sharp drop after 2 failed ADs
- "Adequate" AD trial = maximum tolerable dose for sufficient duration:
  - American Psychiatric Association: 4–8 wks
  - Studies selected for this report: Typically, 6 wks
  - Antidepressant Treatment History Form (ATHF): 4 wks
- Actual time to remission in STAR*D
  - 6.3 wks at Step 1
  - 5.4 wks at Step 2

Background: Treatment of TRD

- AHRQ evidence review (Gaynes et al., 2011)
  - After ≥2 failed ADs, change in pharmacotherapy superior to no change
    - Indirect evidence, overlapping CIs
- 2 SRs: AHRQ (2011); Trivedi et al. (2011)
  - Psychotherapy is effective
  - Psychotherapy vs pharmacotherapy: Unclear
- Disadvantages of multiple AD attempts
  - Diminishing effectiveness
  - Increased risk of adverse events and drug interactions
Background: Treatment of TRD, *neuromodulation*

- ECT
- rTMS
- CES
- ECS
- tDCS
- DBS
- MST
- VNS

CES, cranial electrotherapy stimulation; ECS, epidural cortical stimulation; MST, magnetic seizure therapy; VNS, vagus nerve stimulation

Background: Outcome measurement, depression

- **Response:** Typically, $\geq 50\%$ reduction in depression score
- **Remission:** Score $<\$ specified cutoff
  - E.g., $\leq 8$ on HAM–D$_{17}$, $\leq 10$ on HAM–D$_{21}$, or $\leq 8$ on MADRS
- **Depression scales empirically validated**
  - Definitions of response/remission – convention
- **No standard definition of clinically relevant improvement**
  - Response definition (50% improvement) implies definition of clinical importance
  - 25% improvement $\approx$ partial response $\approx$ MCID

*MCID, minimal clinically important difference*
Background: Outcome measurement, QOL/function

- Global Assessment of Functioning (GAF)
  - Recommended by DSM-IV
  - 0–100, ≤50 signifies severe symptoms and/or psychosocial dysfunction
- SF-36 Health Survey
- World Health Organization Disability Assessment Schedule (WHODAS)
  - An “emerging measure” featured in DSM-V
  - Not used in studies selected for this report
- No standard definition of clinically relevant difference/improvement

Background: Functional relevance of depression scores

- Depression scales
  - Content, e.g., HAM-D
    - Depression symptoms (e.g., mood, guilt, insomnia)
    - Suicide
    - Work/activities
    - Retardation, agitation
    - Somatic symptoms/problems
    - Anxiety, hypochondriasis, depersonalization, paranoia, OCD
  - Validity
    - Comparison w/ “global” measures of depression
    - Comparison w/ other depression scales
- Depression scores vs QOL/function
  - Concordance (low HAM-D vs high QOL), 90% (Pridmore, 2000)
  - Correlation (Hung et al., 2009)
  - Frequency high/low scores (Zimmerman et al., 2012)
  - No mapping of HAM-D to QOL score
## Background: Technology descriptions

<table>
<thead>
<tr>
<th>ECT</th>
<th>tTMS</th>
<th>tDCS</th>
<th>DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrical pulses</td>
<td>Magnetic field</td>
<td>Electrical pulses (compared w/ ECT, lower voltage/current)</td>
<td>Electrical pulses</td>
</tr>
<tr>
<td>Electrode pads on scalp</td>
<td>Electromagnetic core held above skull</td>
<td>Electrode pads on scalp</td>
<td>Implanted electrodes</td>
</tr>
<tr>
<td>Bilateral (bitemporal), unilateral, or bifrontal</td>
<td>Unilateral (left or right DLPFC) or bilateral sequential</td>
<td>Anodal stimulation to left DLPFC, cathodal stimulation to right DLPFC</td>
<td>Direct stimulation of brain tissue.</td>
</tr>
<tr>
<td>Intensity at or just above seizure threshold</td>
<td>High frequency (1-10 Hz), left. Low frequency (≤1 Hz), right.</td>
<td>Intensity: 1 or 2 milliamps of current</td>
<td>Adjustments over wks/mos for optimal stimulation, pulse duration, and amplitude</td>
</tr>
<tr>
<td>Ultrabrief/brief pulse width</td>
<td>Variable frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global stimulation, seizure</td>
<td>Local effects, no seizure. Balances excitability of left/right DLPFC.</td>
<td>Local effects, no seizure. Balances excitability of left/right DLPFC.</td>
<td>Leads stimulate striatum/nucleus accumbens or subcallosal cingulate.</td>
</tr>
<tr>
<td>Inpatient, anesthesia</td>
<td>Outpatient</td>
<td>Outpatient</td>
<td>Implantation surgery for long-term use. Can be switched on/off.</td>
</tr>
<tr>
<td>FDA Class III: Approved for depression</td>
<td>FDA Class II: Cleared for marketing, depression</td>
<td>No FDA decision</td>
<td>FDA Class III: Approved for Parkinson’s, not depression</td>
</tr>
</tbody>
</table>

Concern over safety, efficacy, and cost.

Depression is relatively common and has effects on health, disability, and QOL.
PICO

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

Key questions

- 1a. Are the following nonpharmacologic treatments effective for treatment-resistant depression (TRD)?
  - Electroconvulsive therapy (ECT)
  - Repetitive transcranial magnetic stimulation (rTMS)
  - Transcranial direct current stimulation (tDCS)
  - Deep brain stimulation (DBS)
- 1b. 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?
- 2. What adverse events, including withdrawal from treatment, are associated with nonpharmacologic treatments for TRD, and what are the rates of withdrawal due to lack of benefit?
- 3. 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)?
- 4. What are the cost implications and cost-effectiveness of nonpharmacologic therapies for TRD?
Methods: Searches

- Search for SRs and guidelines
  - All KQs: Core online sources and PubMed, July 2008 to July 2013
  - KQs #1b, #2, #3: Search expanded to include 2003–2008
  - Relevant specialty societies
- Initial search for primary clinical studies (August 1–4, 2013)
  - Starting with end of search time frame in selected SRs
  - Additional search for studies of pts w/ bipolar depression, no date limit
  - PubMed, Ebase, and PsychInfo
  - Excluded Studies list of 2011 AHRQ report
- Search for cost studies (August 2, 2013)
  - National Health Service Economic Evaluation Database (NHS-EED)
  - PubMed
  - Past 10 years
- Final update search: November 12, 2013

Methods: Inclusion/exclusion criteria and quality assessment

- Inclusion criteria varied by technology
  - ECT and rTMS
    - Randomized controlled/comparator trial
    - Observational study, n≥100 (adverse event data)
    - Observational study with comparative data for KQ #3
  - tDCS and DBS
    - Any clinical study
- Exclusion criteria
  - SRs and cost/economic studies published before August 2003
  - No abstract
  - <10 pts
  - For RCTs of rTMS vs sham published after AHRQ report: <43 randomized pts
  - Enrollment not based on TRD and no information suggesting most patients had experienced ≥1 AD failure (some exceptions – KQs #1b, #2, #3)
- Quality assessment
  - Hayes methodology (similar to GRADE)
Search results: 2011 AHRQ evidence review (Gaynes et al., 2011)

- Key source of evidence for ECT and rTMS, KQ #1a (effectiveness)
- Nonpharmacologic treatments for TRD
- Excluded
  - Uncontrolled studies
  - Publication prior to 1980
  - Pts not selected on the basis of TRD or the lack of clinical context suggesting high probability of TRD
- Stated conclusions based on studies where
  - All pts failed ≥2 AD trials
Typical patients in main SRs and RCTs

- Moderate–severe unipolar MDD
- ≥ 2 prior AD failures (where reported)
  - Sometimes specified ≥2 classes
- Failures in current or previous episode?
  - Mixed, rarely reported
- “Adequate” prior AD trial
  - ≥6 wks at maximum tolerable dose, where defined
  - Usually not defined

Findings: ECT
### ECT: KQ #1a (effectiveness)

<table>
<thead>
<tr>
<th>Quantity/Quality, Studies</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Findings</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depression relief, vs sham</strong></td>
<td>Low Study weaknesses Small quantity data Uncertain applicability in 1 study</td>
<td>Favored ECT</td>
<td>Difference in depression score change at end of tx: ~25 vs 18 points on HAM-D17 (0-54 scale) 15.6 vs 1.9 points on BDI (0-63 scale) 18.6 vs 9.6 on HAM-D21 (0-64 scale)</td>
</tr>
<tr>
<td>2 double-blind RCTs (sham); 1 RCT, ECT vs pharmacotx (fair all) 134 pts</td>
<td>--- ---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Suppl data (1 SR; 7 case series, 545 pts) (Heijnen et al., 2010)</td>
<td>--- ---</td>
<td>Pooled rate of remission: 48% (range 39%-63%)</td>
<td></td>
</tr>
<tr>
<td><strong>ECT vs rTMS</strong></td>
<td>Discussed in next section</td>
<td>--- ---</td>
<td>---</td>
</tr>
<tr>
<td>Vs tx as usual, psychotx, tDCS, DBS</td>
<td>Insufficient No data</td>
<td>--- ---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Durability of effect, ECT vs sham</strong></td>
<td>Insufficient 1 very small RCT</td>
<td>Compar- able, 6 mos</td>
<td>---</td>
</tr>
<tr>
<td><strong>QOL/functional status</strong></td>
<td>Insufficient No data</td>
<td>--- ---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Maintenance tx w/ ECT+pharmacotx vs pharmacotx alone</strong></td>
<td>Insufficient Study weaknesses Extremely small quantity data</td>
<td>Favored ECT</td>
<td>Relapse rates: 32% vs 61% (P=0.036); HR, 2.32 (CI, 1.03-5.22)</td>
</tr>
<tr>
<td>1 unblinded RCT (fair) 56 pts</td>
<td>--- ---</td>
<td>---</td>
<td></td>
</tr>
</tbody>
</table>

**BDI, Beck Depression Inventory** © 2014 Winifred S. Hayes, Inc.

### ECT: Clinical relevance, depression outcomes (for indirect comparisons)

<table>
<thead>
<tr>
<th>Source</th>
<th>Change in Score Within Tx Arms</th>
<th>Response * Within Tx Arms</th>
<th>Remission* Within Tx Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAR*D, Step 2 (1 AD failure) (Rush et al., 2006) 1475 pts</td>
<td>---</td>
<td>---</td>
<td>30.6%</td>
</tr>
<tr>
<td>STAR*D, Step 3 (2 AD failures) 622 pts; 2006</td>
<td>---</td>
<td>---</td>
<td>14.3%</td>
</tr>
<tr>
<td>AHRQ (≥2 AD failures) (Gaynes et al., 2011) Pharmacotx arms of 12 RCTs (# pts NR; 1999-2010) Switch: -11.2 Augmentation: -11.2 Maintenance: -7.6 (Scale 0-60, CI overlap.)</td>
<td>Switch: 39.8% Augmentation: 38.1% Maintenance: 27.3% (CI overlap)</td>
<td>Switch: 22.3% Augmentation: 27.2% Maintenance: 16.8% (CI overlap)</td>
<td>---</td>
</tr>
<tr>
<td>ECT arms of selected studies 3 RCTs, 134 pts; 1980-1997 ~25 (0-54 scale) 15.6 (0-63 scale) 18.6 (0-64 scale)</td>
<td>---</td>
<td>---</td>
<td>48% (range 39%-63%)</td>
</tr>
<tr>
<td>Heijnen et al., 2010 SR, 7 case series, 545 pts; 1990-2008</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

*Response, 50% relative improvement. Remission, score at conventional cutoff for scale used. Duration of AD trials: ≤ 14 wks in STAR*D; 4-8 wks, if reported, in other studies.

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### ECT: KQ #1b (effect by tx parameter)

<table>
<thead>
<tr>
<th>Quantity/Quality, Studies</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Findings</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bifrontal stimulation</strong></td>
<td>Low</td>
<td>Mixed</td>
<td><strong>Effect size:</strong></td>
</tr>
<tr>
<td>Dunne et al., 2012 (good SR/MA; 8 double-blind RCTs, but no sham controls)</td>
<td>Lack of sham controls and inconsistency NS pooled effect sizes</td>
<td>Bifrontal vs bitemporal: <strong>0.102</strong>, favoring bifrontal but NS (5 RCTs) Bifrontal vs unilateral: <strong>-0.118</strong>, favoring unilateral but NS (7 RCTs)</td>
<td></td>
</tr>
<tr>
<td><strong>Bilateral vs unilateral</strong></td>
<td>Moderate</td>
<td>Favored bilateral</td>
<td><strong>Effect size:</strong></td>
</tr>
<tr>
<td>UK ECT Review Group, 2003 (fair SR/MA: 22 controlled trials)</td>
<td>Missing detail, study quality, uncertainty in applicability to population of interest</td>
<td>Fixed effects: <strong>-0.323</strong> (CI, -0.446 to -0.199) Random effects: <strong>-0.322</strong> (CI, -0.458 to -0.186)</td>
<td></td>
</tr>
<tr>
<td><strong>High dose vs low dose</strong></td>
<td>Moderate</td>
<td>Favored high dose</td>
<td><strong>Effect size:</strong></td>
</tr>
<tr>
<td>UK ECT Review Group, 2003 (fair SR/MA: 6 controlled trials)</td>
<td>Missing detail, study quality, uncertainty in applicability to population of interest</td>
<td>Fixed effects: <strong>0.571</strong> (CI, 0.352-0.790) (favors higher dose) Random effects: <strong>0.575</strong> (CI, 0.329-0.829)</td>
<td></td>
</tr>
</tbody>
</table>

### ECT: KQ #1b (con’t)

<table>
<thead>
<tr>
<th>Quantity/Quality, Studies</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Findings</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of sessions</strong></td>
<td>Low</td>
<td>Favored 3x/wk over 1x/wk. Favored 2x/wk over 3x/wk but small NS effect.</td>
<td>Results are presented as SES.</td>
</tr>
<tr>
<td>UK ECT Review Group, 2003 (fair SR/MA, 6 RCTs, 210 pts)</td>
<td>Missing detail, study quality Very small quantity of data NS findings</td>
<td>Fixed effects: <strong>0.841</strong> (CI, 0.311 to 1.370) (favors 3x/wk) Random effects: <strong>0.832</strong> (-0.389 to 1.890)</td>
<td></td>
</tr>
<tr>
<td><strong>2x/wk vs 3x/wk (SES)</strong></td>
<td>Moderate</td>
<td>Favored high dose</td>
<td><strong>Effect size:</strong></td>
</tr>
<tr>
<td>(4 trials, 159 pts)</td>
<td>Uncertain applicability to population of interest</td>
<td>Fixed effects: <strong>-0.308</strong> (CI, -0.629 to 0.014) (favors 2x/wk) Random effects: <strong>-0.299</strong> (-0.759 to 1.199)</td>
<td></td>
</tr>
</tbody>
</table>

SES, standardized effect size
ECT: KQ #2 (safety)

- Cognitive decline (low quality)
  - Transient decline over course of tx in some pts (SR: Gardner and O’Connor, 2008, good; SR: Verwijk et al., 2012, fair; pretest/posttest studies)
  - Autobiographical memory loss may persist for several months (Verwijk et al., 2012)
  - Changing tx parameters may reduce effects (very sparse evidence)
  - Depression also diminishes cognitive performance

- Otherwise, generally safe (low quality)
  - No large case series
  - 2 serious events in 3 RCTs: 1 vascular event (retina), 1 tx-emergent mania

- Withdrawal due to lack of benefit (insufficient)
  - 4.3% (ECT) vs 1.4% (sham) (1 RCT, 70 pts)

ECT: KQ #3 (effect by pt factor)

<table>
<thead>
<tr>
<th>Quantity/Quality, Studies</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Findings</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unipolar vs bipolar MDD Dierckx et al., 2012 (fair SR/MA; 6 cohort studies of unknown quality) 1106 pts</td>
<td>Insufficient Inconsistency across studies Heterogeneity in pooled estimate Unknown applicability to the population of interest</td>
<td>No difference</td>
<td>OR of remission, 1.08 (95% CI, 0.75 to 1.57).</td>
</tr>
<tr>
<td>Confirmed TRD vs lack of well-documented AD failure Heijnen et al., 2010 (fair SR/MA; 7 cohort studies w/o tx controls) 958 pts</td>
<td>Low Poor study quality Inconsistency across studies Heterogeneity in pooled estimate (May not be generalizable to current practice of bilateral ECT or high-dose unilateral ECT)</td>
<td>Less effective in confirmed TRD</td>
<td>OR of remission, 0.52 (95% CI, 0.39 to 0.69)</td>
</tr>
</tbody>
</table>

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ECT: KQ #3 (con’t)

<table>
<thead>
<tr>
<th>Subgroups: Psychosis retardation, agitation</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Finding(s)</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post hoc analysis of 2 related RCTs</td>
<td>Low Small quantity data Lack of corroboration by analyses of other trials</td>
<td>Differential effectiveness of ECT according to electrode placement and dose – same in subgroups as overall.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subgroups: Age, race/ethnicity, gender, disease severity, disease duration, symptom type, or comorbidities</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Finding(s)</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient No data</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ECT: KQ #4

› See Findings for rTMS, KQ #4
## ECT: Recap

<table>
<thead>
<tr>
<th>KQ #1a: Depression relief, vs sham (2 RCTs) or psychotx (1 RCT)</th>
<th>Direction of Findings (Quality of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 fair RCTs (134 pts)</td>
<td>Unknown relevance of posttx difference.</td>
</tr>
</tbody>
</table>

**Outcome (# Studies)**

**Direction of Findings (Quality of Evidence)**

<table>
<thead>
<tr>
<th>KQ #1b: Bifrontal (vs unilateral or bilateral [bitemporal])</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SR/MA (8 RCTs)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KQ #1b: Bilateral (vs unilateral)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SR/MA (22 RCTs)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KQ #1b: High dose (vs low dose)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SR/MA (6 RCTs)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KQ #1b: 3x/wk (vs once/wk)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SR/MA (6 RCTs)</td>
<td></td>
</tr>
</tbody>
</table>

*Insufficient evidence for:
- ECT vs usual tx, tDCS, or DBS
- Durability of sham-controlled effect
- Effect on QOL/function

## ECT: Recap (con’t)

<table>
<thead>
<tr>
<th>KQ #2: Safety, vs sham</th>
<th>Direction of Findings (Quality of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(low)</td>
</tr>
</tbody>
</table>

**Outcome (# Studies)**

**Direction of Findings (Quality of Evidence)**

<table>
<thead>
<tr>
<th>KQ #3: Subgroups (psychosis, retardation, agitation):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Differential effectiveness of ECT according to electrode placement and dose</td>
<td></td>
</tr>
</tbody>
</table>

*Post hoc analysis of 2 RCTs*

<table>
<thead>
<tr>
<th>KQ #4: See Findings for rTMS</th>
<th></th>
</tr>
</thead>
</table>

*Uncertain generalizability to current typical tx parameters.
Findings: rTMS

<table>
<thead>
<tr>
<th>Quantity/Quality, Studies</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Findings</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression relief, rTMS vs sham</td>
<td>Moderate Slight inconsistency Favored rTMS</td>
<td>WMD in change scores, depressive severity: 5.92 (CI, –8.15 to –3.70) (I²=80%) (24 RCTs) RR of response in trials requiring ≥1 or ≥2 AD failures: 2.68 (CI, 1.52 to 4.70; NNT=5) (16 RCTs) RR of remission in trials requiring ≥1 or ≥2 AD failures: 3.73 (CI, 1.23 to 11.30; NNT=6) (9 RCTs) (Pooled response/remission rates per group and risk differences NR.)</td>
<td>Study results favored rTMS but differences were not consistently significant</td>
</tr>
</tbody>
</table>

| Durability of benefit, rTMS vs sham | Low Inconsistency Heterogeneity in measurement times | Possibly short-term only | Advantage over sham maintained 2–3 wks (3 RCTs) Inconsistent results at 3–6 mos (5 RCTs) |
rTMS: KQ #1a (con’t)

<table>
<thead>
<tr>
<th>Quantity/Quality, Studies</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Findings</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression relief, rTMS vs ECT</td>
<td>Low Study weaknesses Small volume of data Inconsistency</td>
<td>Comparable or possible superiority of rTMS (2 RCTs)</td>
<td>In the 3 RCTs favoring ECT (significant differences):</td>
</tr>
<tr>
<td>5 RCTs (4 fair, 1 poor)</td>
<td>261 pts</td>
<td>Favored ECT (3 RCTs)</td>
<td>Posttx HAM-D difference: CI, 3.40 to 14.05 (no point estimate)</td>
</tr>
<tr>
<td>Depression relief, rTMS+ECT vs ECT</td>
<td>Low Study weaknesses Sparse data</td>
<td>Comparable</td>
<td>Difference in HAM-D change from BL:</td>
</tr>
<tr>
<td>2 RCTs (fair)</td>
<td>44 pts</td>
<td></td>
<td>36% points</td>
</tr>
<tr>
<td>Vs tx as usual, psychotx, tDCS, DBS</td>
<td>Insufficient No data</td>
<td>---</td>
<td>Risk difference, response: 37% points</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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rTMS: KQ #1a, data published after Final Report, rTMS vs ECT

- 2 MAs suggesting ECT more effective, possibly less tolerable than rTMS
  - Xie et al. (2013)
    - Overall (no heterogeneity)
      - Response: OR, 0.55 (CI, 0.34–0.89); favors ECT (8 RCTs)
      - Remission: OR, 0.49 (CI, 0.29–0.85); favors ECT (7 RCTs)
      - Dropout: OR, 0.70 (CI, 0.36–1.39); favors rTMS (4 RCTs)
    - Subgroup analysis
      - NS differences favoring rTMS for 20 vs 10 Hz, ≥1200 stimuli/session, ≥4 wks of tx
  - Ren et al. (2014) (OR >1 favors ECT)
    - High frequency rTMS vs ECT (no heterogeneity)
      - Response: OR, 1.41 (CI, 1.04–1.90)
      - Remission: OR, 1.38 (CI, 1.10–1.74)
      - Pooled mean score difference: 2.15 (NS)
      - Dropouts: No difference
    - Low frequency rTMS vs ECT (1 RCT): Similar results

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rTMS: KQ #1a (con’t)

<table>
<thead>
<tr>
<th>Quantity/Quality, Studies</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Findings</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOL/Function</td>
<td>Low</td>
<td>Conflicting findings, rTMS vs sham</td>
<td>Improvements, where observed, were very small, i.e., negligible to 2.2 points on 100-point scales</td>
</tr>
<tr>
<td>5 RCTs (at least fair)</td>
<td>Small quantity of data</td>
<td>Inconsistency</td>
<td></td>
</tr>
<tr>
<td>275 pts</td>
<td>Inconsistency</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

rTMS as maintenance tx

| rTMS as maintenance tx | Insufficient No data | --- | --- |

rTMS: Clinical relevance, depression outcomes (for indirect comparisons)

<table>
<thead>
<tr>
<th>Source</th>
<th>Change in Score Within Tx Arms</th>
<th>Response* Within Tx Arms</th>
<th>Remission* Within Tx Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAR*D, Step 2 (1 AD failure) (Rush et al., 2006) 1475 pts</td>
<td>---</td>
<td>---</td>
<td>30.6%</td>
</tr>
<tr>
<td>STAR*D, Step 3 (2 AD failures) 622 pts 2006</td>
<td>---</td>
<td>---</td>
<td>14.3%</td>
</tr>
<tr>
<td>AHRQ (≥ 2 AD failures) (Gaynes et al., 2011) Pharmacologic arms of 12 RCTs (if pts NR, 1999-2010)</td>
<td>Switch: -11.2 Augmentation: -11.2 Maintenance: -7.6 (Scale 0-60. CI overlap.)</td>
<td>Switch: 39.8% Augmentation: 38.1% Maintenance: 27.3% (CI overlap.)</td>
<td>Switch: 22.3% Augmentation: 27.2% Maintenance: 16.8% (CI overlap.)</td>
</tr>
<tr>
<td>rTMS arms of 25 selected RCTs Published 1990s to 2013</td>
<td>15% to 63.2%</td>
<td>12% to 57%</td>
<td></td>
</tr>
</tbody>
</table>

AHRQ/Gaynes et al., 2011: WMD of 5.92 (24 RCTs, rTMS vs sham) using scales of 0 to 52-75 (HAM-D) or 0 to 60 (MADRS).

*Response, 50% relative improvement. Remission, score at conventional cutoff for scale used.
Duration of AD trials: ≤ 14 wks in STAR*D; 4-8 wks, if reported, in other studies.
## rTMS: KQ #1b

<table>
<thead>
<tr>
<th>Quantity/Quality, Studies</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Findings</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral vs unilateral high frequency</td>
<td>Insufficient Small quantity of data inconsistency</td>
<td>Mixed</td>
<td>Response rates (bilateral vs unilateral):</td>
</tr>
<tr>
<td>4 RCTs (sham control in 3 studies; at least fair according to AHRQ or direct assessment)</td>
<td>373 patients</td>
<td></td>
<td>• 20% vs 35% (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 31% vs 48% (P=0.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 38.5% vs 4.5% vs 10% (sham) (global P=0.006)</td>
</tr>
</tbody>
</table>

Compared with sham tx:
- **No increase** in cognitive deterioration (6 fair/good RCTs)
- **No increase** in withdrawal due to adverse events (16 fair/good RCTs)
- **No increase** in seizure (1 case in >38 RCTs)
- **Lower overall rate of withdrawal** (NS difference) (2 fair SR/MAs; Berlim et al., 2013 a and b)
- **Greater incidence** local side effects (mainly discomfort or pain in slap) (7 fair/good RCTs)
- **Greater incidence** (0.73% to 0.84%) treatment-emergent mania (especially bipolar) (1 fair SR/MA)
- **No data**, withdrawal due to lack of benefit
rTMS: KQ #2 (con’t)

- Compared with ECT
  - No overall difference in cognitive effects (3 RCTs)
  - Insufficient evidence regarding withdrawal due to adverse events, overall withdrawals, or specific side effects
- High–vs low–frequency rTMS; bilateral sequential vs unilateral rTMS
  - No difference (4 RCTs)
- Overall conclusions
  - rTMS appears to be safe (moderate quality) (> 38 RCTs)
  - Possibly no difference compared with sham in withdrawal due to lack of benefit (low quality)
    - Indirect evidence based on no difference in overall withdrawal

rTMS: KQ #3

- No association of effect (low quality) with
  - Duration of episode (3 RCTs, 321 pts)
  - Gender (2 RCTs, 122 pts)
  - Unipolar vs bipolar depression (very indirect evidence, stratified analysis, AHRQ/Gaynes et al., 2011 MA)
  - Degree of medication resistance
    - No difference in 1 RCT
    - Somewhat smaller pooled estimates for ≥1 AD failure than for ≥2 AD failures, AHRQ/Gaynes et al. MA; overlapping CIs suggest NS difference
- Conflicting evidence from small trials, or no evidence (insufficient): age, race/ethnicity, disease severity, symptom type, comorbidities, or history of prior ECT
rTMS: KQ #4, Simpson et al., 2009 (rTMS vs pharmacotherapy)

- Markov model, U.S. healthcare system/societal perspectives, 1 yr
- rTMS cost and effectiveness data from 3 related trials (original trial: O'Reardon et al., 2007, fair–good quality).
- Trials and economic evaluation sponsored by manufacturer
- Effectiveness of pharmacotherapy from STAR*D
- rTMS vs pharmacotherapy: Cost saving, both perspectives
  - Cost savings greater in subgroup with lowest level of medication resistance
- Weaknesses
  - Numerous reporting omissions
  - Possible methodological weaknesses
  - No sensitivity analysis of effectiveness estimate

rTMS: KQ #4, Kozel et al., 2004 (rTMS vs ECT)

- Decision analysis, U.S. societal perspective, 1 yr
- Source of effectiveness estimate: Grunhaus et al., 2000
- ECT for acute and maintenance tx vs rTMS for acute and maintenance tx
  - Incremental cost–effectiveness ratio (ICER): $460,031*/QALY (base year unclear)
- rTMS–then–ECT–for–nonresponders
  - Dominated ECT alone
- (rTMS–then–ECT–for–nonresponders vs rTMS alone
  - $31,783/QALY*)
- Weakness: Limited (1–way) sensitivity analysis

*Costs assumed to be collected 2004 or earlier
rTMS: KQ #4, Knapp et al., 2008 (rTMS vs ECT)

- Trial-based, UK national health/social services and societal perspectives, 6 mos
- Cost and effectiveness estimates: Eranti et al., 2007/McLoughlin et al., 2007 (fair quality)
  - Remission at end of tx: 17% vs 59% (P=0.05)
  - HAM-D at 6 mos: 23.9 vs 24.8 (NS)
  - QALY gains at 6 mos: 0.03000 vs 0.0297 (NS)
  - Total societal cost at 6 mos: £10,632 vs £6303
- Cost–effectiveness acceptability curve (CEAC)
  - 98% probability that cost per unit difference in 6-mo HAM-D score would not exceed ~$921* (health/social services costs only) or ~$1290* (societal perspective)
  - Probability of ICER < £30,000 ($55,282/QALY*): 13% to 22%
- Strength: Cost and QALY data collected in same trial
- Weaknesses: No inclusion of work loss; no transportation costs for ECT

*Conversion of results or threshold in £, assuming price year of 2004, to 2013 USD.

---

rTMS: Recap

<table>
<thead>
<tr>
<th>Outcome (# Studies)</th>
<th>Direction of Findings (Quality of Evidence)</th>
</tr>
</thead>
</table>
| KQ #1a*: Depression relief, vs sham  
1 MA (good; 24 fair/good RCTs); 3 additional fair RCTs | (moderate)  
Unknown relevance, posttx difference |
| KQ #1a: Durability of benefit, vs sham  
7 RCTs (fair/good) | (low)  
Possibly only 2-3 wks |
| KQ #1a: Depression relief, vs ECT  
5 RCTs (4 fair, 1 poor) | (low)  
Mixed, may depend on tx parameters and strategy |
| KQ #1a: Depression relief, rTMS+ECT vs ECT  
2 RCTs (fair) | (low)  
| KQ #1a: QOL/function  
5 RCTs (at least fair) | ?  
Conflicting findings, rTMS vs sham  
Comparable, rTMS vs ECT or rTMS+ECT vs ECT |

*Insufficient evidence for rTMS vs usual bx, psychotx, tDCS, or DBS.
rTMS: Recap (con’t)

<table>
<thead>
<tr>
<th>Outcome (# Studies)</th>
<th>Direction of Findings (Quality of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ #2: Overall safety, vs sham or ECT (≥16 RCTs w/ explicit safety data; &gt;38 RCTs overall; fair/good quality)</td>
<td>(moderate) Scalp discomfort/pain common but transient. No other risks.</td>
</tr>
<tr>
<td>KQ #2: Withdrawal due to lack of benefit, vs sham (indirect evidence from 2 SRs/MAs)</td>
<td>(low)</td>
</tr>
<tr>
<td>KQ #3: Duration of episode/depression relief, vs sham (3 RCTs)</td>
<td>(low)</td>
</tr>
<tr>
<td>KQ #3: Gender/depression relief, vs sham (2 RCTs)</td>
<td>(low)</td>
</tr>
<tr>
<td>KQ #3: Unipolar vs bipolar/depression relief, vs sham (very indirect evidence, stratified analysis, AHRQ MA)</td>
<td>(low)</td>
</tr>
<tr>
<td>KQ #3: Degree of medication resistance/depression relief, vs sham (1 RCT; indirect evidence, stratified analysis, AHRQ MA)</td>
<td>(low)</td>
</tr>
</tbody>
</table>

rTMS: Recap, KQ #4

<table>
<thead>
<tr>
<th>Comparison (Study Author; Country)</th>
<th>Results/Conclusion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>rTMS vs pharmacotherapy</td>
<td>rTMS was cost saving</td>
<td>Reporting omissions diminish confidence in conclusions</td>
</tr>
<tr>
<td>(Simpson et al., 2009; U.S.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECT acute and maintenance vs rTMS acute and maintenance (Kozel et al., 2004; U.S.)</td>
<td>$460,031/QALY</td>
<td>ECT more expensive Multiple data sources w/ extrapolation 1-way sensitivity analysis (no simultaneous variance of rTMS and ECT effectiveness)</td>
</tr>
<tr>
<td>rTMS-then-ECT-for-nonresponders vs ECT alone (Kozel et al., 2004; U.S.)</td>
<td>rTMS-then-ECT-for-nonresponders dominated</td>
<td></td>
</tr>
<tr>
<td>rTMS vs ECT (Knapp et al., 2004; UK)</td>
<td>Unlikely rTMS would be considered cost-effective</td>
<td>rTMS more expensive Cost and QALY data from same trial No inclusion of work loss; no transportation costs for ECT</td>
</tr>
</tbody>
</table>
Findings: tDCS

<table>
<thead>
<tr>
<th>Quantity/Quality, Studies</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Findings</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression relief, vs sham</td>
<td>Low Small quantity of data Inconsistency Imprecision</td>
<td>Favored tDCS (NS, pooled response and remission)</td>
<td>Pooled tDCS-vs-sham effect size based on % change from baseline: 0.74 (CI, 0.21 to 1.27; P=0.006); 6 RCTs (Kalu et al., 2012)</td>
</tr>
<tr>
<td>2 MAs (1 good [Berlim et al., 2013c], 1 fair [Kalu et al., 2012]), including 7 RCTs</td>
<td></td>
<td></td>
<td>Pooled response (tTMS, sham, pooled OR): 23.2%, 12.4%, 1.97 (95% CI, 0.85 to 4.56; P=0.11); 6 RCTs (Berlim et al., 2013c)</td>
</tr>
<tr>
<td>1 additional RCT (good)</td>
<td></td>
<td></td>
<td>Pooled Remission (tDCS, sham, pooled OR): 12.2%, 5.4%, 2.13 (9.5% CI, 0.64 to 7.06; P=0.22); 6 RCTs (Berlim et al., 2013c) NNT 10*</td>
</tr>
<tr>
<td>320 pts total</td>
<td></td>
<td></td>
<td>Difference, mean MADRS (tDCS vs sham): -5.6 (CI, -1.30 to -10.01; P=0.01) (1 RCT)</td>
</tr>
</tbody>
</table>

*Calculated on the basis of rate data supplied by the authors.

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## tDCS: KQ #1a (con’t)

<table>
<thead>
<tr>
<th>Quantity/Quality, Studies</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Findings</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durability of benefit</td>
<td>Insufficient</td>
<td>Sustained or additional benefit up to 1 mo</td>
<td>Positive results maintained at 1 mo (1 RCT, 2 case series) Difference increased in favor of tDCS (1 RCT)</td>
</tr>
<tr>
<td>Maintenance tx w/ continuing tDCS</td>
<td>Insufficient</td>
<td>Sustained or additional benefit</td>
<td>Response persisted mean 11.7 wks (1 RCT); reduction in symptom scores increased (1 RCT)</td>
</tr>
<tr>
<td>QOL/function</td>
<td>Insufficient</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

### tDCS: Clinical relevance, depression outcomes (for indirect comparisons)

<table>
<thead>
<tr>
<th>Source</th>
<th>Change in Score Within Tx Arms</th>
<th>Response* Within Tx Arms</th>
<th>Remission* Within Tx Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAR*D, Step 2 (1 AD failure)</td>
<td>---</td>
<td>---</td>
<td>30.6%</td>
</tr>
<tr>
<td>(Rush et al., 2006)</td>
<td>1475 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAR*D, Step 3 (2 AD failures)</td>
<td>---</td>
<td>---</td>
<td>14.3%</td>
</tr>
<tr>
<td>(2006)</td>
<td>622 pts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHRQ (≥2 AD failures)</td>
<td>Switch: -11.2</td>
<td>Switch: 39.8%</td>
<td>Switch: 22.3%</td>
</tr>
<tr>
<td>Pharmacotx arms of 12 RCTs (if pts NR): 1999-2010</td>
<td>Augmentation: -11.2</td>
<td>Augmentation: 38.1%</td>
<td>Augmentation: 27.2%</td>
</tr>
<tr>
<td>Maintenance: -7.6</td>
<td>(Scale 0–60; CI overlap.)</td>
<td>Maintenance: 27.3%</td>
<td>Maintenance: 16.8%</td>
</tr>
<tr>
<td>AHRQ/Gaynes et al., 2011: WMD of 5.92 (24 RCTs, rTMS vs sham) using scales of 0 to 52-75 (HAM-D) or 0 to 60 (MADRS).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berlim et al., 2013c</td>
<td>23.2%</td>
<td>12.2%</td>
<td></td>
</tr>
<tr>
<td>tDCS arms of 6 RCTs, 201 pts; 2006-2012</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Response: 50% relative improvement. Remission: score at conventional cutoff for scale used. Duration of AD trials: ≤ 14 wks in STAR*D; 4-8 wks, if reported, in other studies.
tDCS: KQ #1b

- Insufficient evidence (conflicting results between 2 SRs/MAs; Kalu et al., 2012; Berlim et al., 2013c)
  - Number of sessions
  - Strength of current
  - Concurrent use of ADs

- Itching (1 good SR/MA, 117 studies) (Brunoni et al., 2011a)
  - 39.3% tDCS vs 32.9% sham

- No serious events in 2 other SRs/MAs (Kalu et al., 2012; Berlim et al., 2013c)

- Treatment-induced hypomania
  - 7% in study populations with minority of bipolar pts (3 RCTs)
  - 3%-17% in tDCS arms, unipolar MDD only (1 RCT)

- Dropout (1 SR/MA) (Berlim et al., 2013c)
  - 5.8% tDCS vs 5.2% sham

Overall conclusions
- tDCS appears to be safe (moderate quality)
- Withdrawal due to lack of benefit may not differ between tDCS and sham (low quality).
tDCS: KQ #3

- Baseline severity
  - No association w/ depression relief (Kalu et al., 2012; fair SR/MA, 6 fair RCTs; metaregression)
  - Low quality
- Age, gender, unipolar vs bipolar depression
  - Not predictive of response in case series
  - Insufficient evidence (case series)
- Race/ethnicity, disease duration, symptom type, comorbidities, and number and type of prior treatments
  - Insufficient evidence (no data or single small trials)

---

**tDCS: Recap**

<table>
<thead>
<tr>
<th>Outcome (# Studies)</th>
<th>Direction of Findings (Quality of Evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ #1a*: Depression relief, vs sham (2 fair-good SRs/MAs, 7 fair RCTs; 1 additional good RCT)</td>
<td><img src="low" alt="Small posttx differences; some NS." /></td>
</tr>
<tr>
<td>KQ #2: Overall safety, vs sham (3 SRs/MAs)</td>
<td><img src="moderate" alt="Generally safe." /> Itching common, transient. Possible small risk, hypomania.</td>
</tr>
<tr>
<td>KQ #2: Withdrawal due to lack of benefit, vs sham (indirect evidence from 1 SR/MA)</td>
<td><img src="low" alt="" /></td>
</tr>
<tr>
<td>KQ #3: Baseline severity, depression relief (1 fair SR/MA, 6 fair RCTs)</td>
<td><img src="low" alt="" /></td>
</tr>
</tbody>
</table>

*Insufficient evidence for:*
- tDCS vs usual tx, psychotx, ECT, rTMS, or DBS
- Durability of sham-controlled effect
- Effect on QOL/function

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Findings: DBS

<table>
<thead>
<tr>
<th>Quantity/Quality, Studies</th>
<th>Quality, Body of Evidence</th>
<th>Direction of Findings</th>
<th>Magnitude of Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression relief, vs sham</td>
<td>Insufficient Small quantity of data Poor/very poor studies</td>
<td>Improvement w/ respect to BL*</td>
<td>Response rate: 40%-60% at 6 mos (4 studies); 25%-55% at 12 mos (3 studies). Remission rate: 18%-35% at 6 mos (3 studies); 18%-36% at 12 mos (2 studies)</td>
</tr>
<tr>
<td>Durability of benefit</td>
<td>Insufficient Small quantity of data Poor/very poor studies Inconsistency Variable</td>
<td>Improvement vs decline after 6 mos was inconsistent across studies.</td>
<td></td>
</tr>
<tr>
<td>QOL/function</td>
<td>Insufficient for very small quantity of data and poor/very poor studies</td>
<td>Improvement w/ respect to BL*</td>
<td>Increase in GAF score: 18.4 points at 2 yrs (P&lt;0.0009); 28.3 points at 1 yr (P&lt;0.001) (1–100 scale)</td>
</tr>
</tbody>
</table>

*But no difference in improvement in 1 study during 4 wks of active stimulation compared with improvement during 4 wks of sham stimulation.
DBS: KQ #1b

- Insufficient evidence
  - No differences detected in small number of poor-quality studies

- Serious device-related events possible; treatment-emergent rate of somatic events uncertain
- Narrative review
  - Hemorrhage in 10% pts
- Poor-quality SR of 546 studies, ≤10,339 pts (any indication) (Appleby et al., 2007)
  - Of 6574 reported device-related events
    - Infection, 16%; explantation, 15%; lead fracture, 15%; erosion, 14%
  - Of 6573 reported somatic adverse events
    - No type of event occurred in ≥5% pts
    - 4 non-suicide deaths; 11 completed suicides
- 2 SRs of DBS (any psychiatric indication) (Bergfeld et al., 2013, fair; Duits et al., 2013, poor)
  - Cognitive decline was minimal and/or transient
- 5 uncontrolled studies (86 pts) selected for this report
  - Infection the only common event (5%-20% in 3 studies)
- Overall conclusion: Insufficient evidence

DBS: KQ #2
DBS: KQ #3

- **Insufficient** evidence
  - A single uncontrolled study evaluated certain response predictors
  - No controlled studies

DBS: Recap

- Evidence for all KQs was insufficient (very low quality or nonexistent)
### Practice Guidelines and Payer Policies

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Relevant Recommendations</th>
<th>Quality *</th>
</tr>
</thead>
<tbody>
<tr>
<td>APA - MDD (2010)</td>
<td>No definition of TRD. *Numerous&quot; failures of adequate AD trials is a factor when considering ECT. ECT: The most effective acute phase tx for pts for whom medication and/or psychoct have been ineffective and may be offered during the continuation phase. rTMS may be considered; less evidence than for ECT.</td>
<td>5 (fair)</td>
</tr>
<tr>
<td>APA - Bipolar (2002; 2005)</td>
<td>No definition of TRD. ECT may be considered for severe or tx-resistant bipolar depression.</td>
<td>5 (fair)</td>
</tr>
<tr>
<td>CANMAT – MDD (Kennedy et al., 2009)</td>
<td>No definition of TRD ECT is recommended for first-line tx for acute suicidal ideation, MDD with psychotic features, or TRD (Level 1 evidence) and for certain other indications (Level 3). Recommended as second-line treatment for patients who are otherwise treatment-resistant or who have medication intolerance. rTMS is recommended for second-line treatment (Level 1 for acute treatment and safety; Level 3 for relapse prevention). DBS is considered investigational.</td>
<td>5 (fair)</td>
</tr>
<tr>
<td>CANMAT – Bipolar (Yatham et al., 2013)</td>
<td>For depression in BD II (periods of hypomania and depression), ECT is recommended after failure of 3 prior AD trials, and for BD I (periods of mania and depression), as a third-line tx.</td>
<td>3 (poor)</td>
</tr>
</tbody>
</table>

*Scale of 1 to 7 and judged to be good (6–7), fair (4–5), or poor (1–3). APA, American Psychiatric Society; BD, bipolar depression; CANMAT, Canadian Network for Mood and Anxiety Treatments
### Practice guidelines (con’t)

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Relevant Recommendations</th>
<th>Quality</th>
</tr>
</thead>
</table>
| ICSI (2012)        | **ADs and/or referral for psychotx for MDD.**  
TRD defined as failure to achieve remission (HAM-D17 < 7 or PHQ-9 < 5) after 3 different classes of ADs.  
ECT, phototherapy, augmentation strategies, and hospitalization recommended for TRD. ECT may be recommended for special cases (see text).                                                                                                           | 6 (good) |
| NICE (2009)        | **No definition of TRD.**  
A combination of AD medication and CBT is recommended for pts who have not responded to drugs or psychotx.  
ECT is recommended for severe depression when other tx methods have failed. The routine use of ECT for moderate depression is not recommended, unless depression has not responded to multiple drug and psychological txs.  
**rTMS should be reserved for research purposes only** because of uncertainty about clinical efficacy.                                                                                                                                    | 7 (good) |

*Scale of 1 to 7 and judged to be good (6-7), fair (4-5), or poor (1-3).

CBT, cognitive behavioral therapy; ICSI, Institute for Clinical Systems Improvement; NICE, National Institute for Health and Care Excellence; PHQ, Patient Health Questionnaire

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### Practice guidelines (con’t)

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Relevant Recommendations</th>
<th>Quality</th>
</tr>
</thead>
</table>
| VA/DoD † (2009)    | Pts who do not respond to pharmacotx w/ a single agent may receive combination tx w/ pharmacotx and CBT or IPT.  
Pts who have not responded to 2 first–line ADs should either be switched to a new AD from a different class (venlafaxine is recommended, if not already tried) or receive augmentation w/ either medications or psychotx.  
**Pts who have not responded to 3 different ADs should either receive augmentation w/ medications or psychotx or receive combination AD tx or ECT.**  
Response/remission should be assessed at 8–12 wks after initiation of each new strategy.  
Significant response defined as 5–point reduction or score ≤ 10 on PHQ—9 or ≤ 25% reduction in score on an accepted standardized instrument.  
Remission defined as PHQ—9 ≤ 4, BDI ≤ 10, or HAM—D17 ≤ 7, maintained for ≥ 1 mo.                                                                                                            | 6 (good) |

*Scale of 1 to 7 and judged to be good (6-7), fair (4-5), or poor (1-3).

DoD, Department of Defense; IPT, interpersonal therapy; VA, Veterans Administration
Practice guidelines: recap

<table>
<thead>
<tr>
<th>Guideline Sponsor</th>
<th>ECT</th>
<th>rTMS</th>
<th>tDCS</th>
<th>DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>APA</td>
<td>Recommended for TRD (unipolar and bipolar)</td>
<td>May be considered for TRD</td>
<td>No recommendation</td>
<td>No recommendation</td>
</tr>
<tr>
<td>CANMAT</td>
<td>Recommended for TRD (unipolar and bipolar)</td>
<td>Recommended for TRD (unipolar)</td>
<td>No recommendation</td>
<td>Investigational</td>
</tr>
<tr>
<td>ICSI</td>
<td>Recommended for TRD</td>
<td>No recommendation</td>
<td>No recommendation</td>
<td>No recommendation</td>
</tr>
<tr>
<td>NICE</td>
<td>Recommended for TRD</td>
<td>For research only</td>
<td>No recommendation</td>
<td>No recommendation</td>
</tr>
<tr>
<td>VA/DoD</td>
<td>Recommended for TRD</td>
<td>No recommendation</td>
<td>No recommendation</td>
<td>No recommendation</td>
</tr>
</tbody>
</table>

Selected payer policies

<table>
<thead>
<tr>
<th>Payer</th>
<th>ECT</th>
<th>rTMS</th>
<th>tDCS</th>
<th>DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aetna</td>
<td>Covered for medication resistance; unipolar, bipolar, mixed episode depression</td>
<td>Not covered</td>
<td>No policy</td>
<td>Not covered</td>
</tr>
<tr>
<td>CMS</td>
<td>No NCD</td>
<td>No NCD</td>
<td>No NCD</td>
<td>No NCD</td>
</tr>
<tr>
<td>Regence</td>
<td>No policy</td>
<td>Not covered</td>
<td>No policy</td>
<td>Not covered</td>
</tr>
<tr>
<td>Group Health</td>
<td>No policy</td>
<td>Not covered</td>
<td>No policy</td>
<td>No policy</td>
</tr>
<tr>
<td>New England CEPAC</td>
<td>Evidence is inadequate</td>
<td>Equivalent to or superior to ECT and to usual care</td>
<td>No evaluation</td>
<td>No evaluation</td>
</tr>
<tr>
<td>OR HERC</td>
<td>For MDD after failure ≥2 AD txs</td>
<td>For MDD after failure ≥ 2 AD txs</td>
<td>No evaluation</td>
<td>No evaluation</td>
</tr>
</tbody>
</table>

CEPAC, Comparative Effectiveness Public Advisory Council; HERC, Health Evidence Review Commission; NCD, National Coverage Determination

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## Final Summary

### Final Summary: Direction/Quality of Overall Findings

<table>
<thead>
<tr>
<th>KQ</th>
<th>ECT</th>
<th>rTMS</th>
<th>IDCS</th>
<th>DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1a: Effective vs sham?*</td>
<td>Depression: Yes (low)</td>
<td>Depression: Yes (moderate)</td>
<td>Depression: Yes (low)</td>
<td></td>
</tr>
<tr>
<td>vs other nonpharm tx?</td>
<td>See rTMS</td>
<td>rTMS vs ECT: Mixed results</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>vs usual care or pharmacotx?</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>#1b: Effect varies by tx parameter?</td>
<td>Bifrontal = Uni/bitemp (low)</td>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral &gt; Uni (moderate)</td>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High dose &gt; Low dose (moderate)</td>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#2: Safe?</td>
<td>Overall, yes (low)</td>
<td>Overall, yes (moderate)</td>
<td>Safe (low)</td>
<td></td>
</tr>
<tr>
<td>#3: Effect varies by pt factor?</td>
<td>Confirmed TRD &lt; Unclear med history (low)</td>
<td>Duration of episode, gender; yes vs bipolar, degree of medication resistance</td>
<td>Baseline severity; No association (low)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No association w/ psychosis, agitation, depression (low)</td>
<td>No association (low)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#4</td>
<td>rTMS vs AD: May be cost saving (1 study)</td>
<td>ECT vs rTMS: No cost-effective, rTMS then-ECT for nonresponder; Dominates ECT alone (1 study)</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECT vs rTMS: No cost-effective (1 study)</td>
<td>I</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

* Clinical relevance uncertain

---

Bitemp, bitemporal (bilateral); fxn, function; I, insufficient evidence; uni, unilateral
Gaps in the evidence

- Trials of sufficient size and design to determine the efficacy of tDCS and DBS.
- More randomized comparator trials addressing specific options for the manner in which treatments are delivered.
- RCTs and cohort studies powered to demonstrate differential effectiveness and safety according to patient characteristics.
- Additional cost-effectiveness analyses.
- Trials comparing the technologies of interest with active treatment.
- A standard definition of TRD with criteria for judging the adequacy of previous AD trials, acknowledgment that AD failure can be due to intolerable side effects, and clarification of whether lifetime AD trials or only AD trials that took place in the current episode should be considered.
- More uniform reporting of all 3 forms of symptom outcomes: score change, response rate, and remission rate.
- Empirically derived definitions of clinically relevant improvement, response, and remission in patients with MDD.

Thank you.
Links to Supporting Materials

Nonpharmacologic Treatments for Treatment-Resistant Depression

Prepared 3-3-14

References:


Isenberg K, Downs D, Pierce K, et al. Low frequency rTMS stimulation of the right frontal cortex is as effective as high frequency rTMS stimulation of the left frontal cortex for antidepressant-free, treatment-resistant depressed patients. *Ann Clin Psychiatry*. 2005;17(3):153-159. PMID 16433057.


Pridmore S. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in a course of electroconvulsive therapy. Depress Anxiety. 2000;12(3):118-123. PMID 11126185.


Smarr KL, Keefer AL. Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). *Arthritis Care Res.* 2011;63(S11):S454-S466. PubMed [22588766](https://pubmed.ncbi.nlm.nih.gov/22588766/).


Substance Abuse and Mental Health Services Administration (SAMHSA). Patient Health Questionnaire (PHQ-9). SAMHSA-HRSA Center for Integrated Health Solutions. October 4, 2005. Available at:


Systematic Reviews Published after Update Search for Final Report


Outcome Measurement Tools:

Hamilton Rating Scale for Depression (HAM-D): http://healthnet.umassmed.edu/mhealth/HAMD.pdf

Montgomery-Åsberg Depression Rating Scale (MADRS): www.sfaetc.ucsf.edu/docs/MADRS.pdf
To find best outcomes and value for the state and the patient, the HTA program focuses on three questions:

1. Is it safe?
2. Is it effective?
3. Does it provide value (improve health outcome)?

The principles HTCC uses to review evidence and make determinations are:

**Principle One: Determinations are Evidence based**

HTCC requires scientific evidence that a health technology is safe, effective and cost-effective as expressed by the following standards:

- Persons will experience better health outcomes than if the health technology was not covered and that the benefits outweigh the harms.
- The HTCC emphasizes evidence that directly links the technology with health outcomes. Indirect evidence may be sufficient if it supports the principal links in the analytic framework.
- Although the HTCC acknowledges that subjective judgments do enter into the evaluation of evidence and the weighing of benefits and harms, its recommendations are not based largely on opinion.
- The HTCC is explicit about the scientific evidence relied upon for its determinations.

**Principle Two: Determinations result in health benefit**

The outcomes critical to HTCC in making coverage and reimbursement determinations are health benefits and harms:

- In considering potential benefits, the HTCC focuses on absolute reductions in the risk of outcomes that people can feel or care about.
- In considering potential harms, the HTCC examines harms of all types, including physical, psychological, and non-medical harms that may occur sooner or later as a result of the use of the technology.
- Where possible, the HTCC considers the feasibility of future widespread implementation of the technology in making recommendations.
- The HTCC generally takes a population perspective in weighing the magnitude of benefits against the magnitude of harms. In some situations, it may make a determination for a technology with a large potential benefit for a small proportion of the population.
- In assessing net benefits, the HTCC subjectively estimates the indicated population's value for each benefit and harm. When the HTCC judges that the balance of benefits and harms is likely

---

1 Based on Legislative mandate: See RCW 70.14.100(2).
to vary substantially within the population, coverage or reimbursement determinations may be more selective based on the variation.

- The HTCC considers the economic costs of the health technology in making determinations, but costs are the lowest priority.

### Using Evidence as the Basis for a Coverage Decision

Arrive at the coverage decision by identifying for Safety, Effectiveness, and Cost whether (1) evidence is available, (2) the confidence in the evidence, and (3) applicability to decision.

1. **Availability of Evidence:**

   Committee members identify the factors, often referred to as outcomes of interest, that are at issue around safety, effectiveness, and cost. Those deemed key factors are ones that impact the question of whether the particular technology improves health outcomes. Committee members then identify whether and what evidence is available related to each of the key factors.

2. **Sufficiency of the Evidence:**

   Committee members discuss and assess the evidence available and its relevance to the key factors by discussion of the type, quality, and relevance of the evidence using characteristics such as:

   - Type of evidence as reported in the technology assessment or other evidence presented to committee (randomized trials, observational studies, case series, expert opinion);
   - The amount of evidence (sparse to many number of evidence or events or individuals studied);
   - Consistency of evidence (results vary or largely similar);
   - Regency (timeliness of information);
   - Directness of evidence (link between technology and outcome);
   - Relevance of evidence (applicability to agency program and clients);
   - Bias (likelihood of conflict of interest or lack of safeguards).

   Sufficiency or insufficiency of the evidence is a judgment of each clinical committee member and correlates closely to the GRADE confidence decision.

<table>
<thead>
<tr>
<th>Not Confident</th>
<th>Confident</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.</td>
<td>Very certain of evidentiary support. Further information is unlikely to change confidence</td>
</tr>
</tbody>
</table>

---

4 Based on GRADE recommendation: [http://www.gradeworkinggroup.org/FAQ/index.htm](http://www.gradeworkinggroup.org/FAQ/index.htm)
3. **Factors for Consideration - Importance**

At the end of discussion a vote is taken on whether sufficient evidence exists regarding the technology’s safety, effectiveness, and cost. The committee must weigh the degree of importance that each particular key factor and the evidence that supports it has to the policy and coverage decision. Valuing the level of importance is factor or outcome specific but most often include, for areas of safety, effectiveness, and cost:

- Risk of event occurring;
- The degree of harm associated with risk;
- The number of risks; the burden of the condition;
- Burden untreated or treated with alternatives;
- The importance of the outcome (e.g. treatment prevents death vs. relief of symptom);
- The degree of effect (e.g. relief of all, none, or some symptom, duration, etc.);
- Value variation based on patient preference.
Medicare Coverage and Guidelines

From pages 25-27 of the evidence report

Selected Payer Policies and Policy Guidance

See Selected Payer Policies in the TECHNICAL REPORT for additional detail and links to policy documents.

Electroconvulsive Therapy (ECT)
ECT is covered by Aetna for unipolar, bipolar, or mixed episode major depression under any of several very specific conditions, including lack of response to effective medication given for an adequate dose and duration (number of trials unspecified), favorable response to ECT in the past, or pregnancy. The Oregon Health Evidence Review Commission (HERC) recommends coverage of ECT for an episode of major depressive disorder (MDD) in patients who have failed ≥ 2 pharmacologic treatments. The New England Comparative Effectiveness Public Advisory Council (CEPAC) has concluded that the evidence is inadequate to support a conclusion that ECT is equivalent or superior to usual care for TRD.

No National Coverage Determination (NCD) by the Centers for Medicare & Medicaid Services (CMS) and no policies on the website for GroupHealth or Regence Group were identified.

Repetitive Transcranial Magnetic Stimulation (rTMS)
Aetna, GroupHealth, and Regence Group have noncoverage policies for rTMS. The Oregon HERC recommends coverage of rTMS for patients with an episode of MDD who have failed ≥ 2 pharmacologic treatments. No NCD by CMS was identified. The New England CEPAC has concluded that rTMS is equivalent or better than both usual care and ECT as a treatment for TRD.

Transcranial Direct Current Stimulation (tDCS)
No policies or statements on tDCS could be identified on the Aetna, CMS, GroupHealth, Oregon HERC, or Regence Group website. This technology has not been addressed by The New England CEPAC.

Deep Brain Stimulation (DBS)
Aetna and Regence Group have noncoverage policies regarding DBS for depression. No policies or statements on DBS for depression could be identified on the CMS, GroupHealth, or Oregon HERC website. This technology has not been addressed by The New England CEPAC.
Table 6. Summary of Practice Guidelines

Key: AD, antidepressant (medication); APA, American Psychiatric Association; BD, bipolar disorder; BDI, Beck Depression Inventory; CANMAT, Canadian Network for Mood and Anxiety Treatments; CBT, cognitive-behavioral therapy; ECT, electroconvulsive therapy; HAM-D, Hamilton Depression Rating Scale; ICSI, Institute for Clinical Systems Improvement; IPT, interpersonal therapy; MDD, major depressive episode; NICE, National Institute for Health and Care Excellence; NR, not reported; PHQ, Patient Health Questionnaire; pt(s), patient(s); rTMS, transcranial magnetic stimulation; TRD, treatment-resistant depression; tx, treatment; VA/DoD, Veterans Affairs and the Department of Defense; VNS, vagus nerve stimulation

<table>
<thead>
<tr>
<th>Sponsor, Title</th>
<th>Relevant Recommendations</th>
<th>Quality* / Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>APA (2010) (MDD)</td>
<td>No definition of TRD, but guidelines imply that combination psychotherapy and AD medication should be tried before other txs are considered and cite “numerous” ineffective but adequately designed medication trials as a factor to take into account when considering ECT (e.g., pt considering suicide). ECT is considered the most effective acute phase tx for pts for whom medication and/or psychotherapy have been ineffective as acute phase txs and may be offered during the continuation phase; see text for other considerations. Light therapy is another option when medication and psychotherapy have failed. rTMS may be considered; less evidence than for ECT.</td>
<td>5 (no critical appraisal of evidence and unclear link between quality/quantity of evidence and recommendations)</td>
</tr>
<tr>
<td>APA (2002); APA (2005) (BD)</td>
<td>No definition of TRD. ECT may be considered for severe or tx-resistant bipolar depression.</td>
<td>5 (no critical appraisal of evidence and unclear link between quality/quantity of evidence and recommendations)</td>
</tr>
<tr>
<td>CANMAT (2009) (MDD)</td>
<td>No definition of TRD. ECT is recommended for first-line tx for acute suicidal ideation, MDD with psychotic features, or TRD (Level 1 evidence) and for certain other indications (Level 3). Recommended as second-line treatment for patients who are otherwise treatment-resistant or who have medication intolerance. rTMS is recommended for second-line treatment (Level 1 for acute treatment and safety; Level 3 for relapse prevention). DBS is considered investigational.</td>
<td>5 (intended pt population for rTMS and whether it may be considered in the absence of failed ECT were unclear)</td>
</tr>
<tr>
<td>CANMAT (2013) (BD)</td>
<td>For depression in BD II (periods of hypomania and depression), ECT is recommended after failure of 3 prior AD trials, and for BD I (periods of mania and depression), as a third-line tx.</td>
<td>3 (no linking of recommendations w/ evidence)</td>
</tr>
<tr>
<td>ICSI (2012)</td>
<td>No definition of TRD. ADs and/or referral for psychotherapy for MDD. TRD defined as failure to achieve remission (HAM-D$_{17}$ &lt;7 or PHQ-9 &lt;5) after 3 different classes of ADs. ECT, phototherapy, augmentation strategies, and hospitalization recommended for TRD. ECT may be recommended for special cases (see text).</td>
<td>6 (criteria for selecting evidence was not reported; body of evidence limitations NR; methods for formulating recommendations was NR)</td>
</tr>
<tr>
<td>Sponsor, Title</td>
<td>Relevant Recommendations</td>
<td>Quality* / Comments</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>NICE (2009)</td>
<td>No definition of TRD. A combination of AD medication and CBT is recommended for pts who have not responded to drugs or psychotherapy. ECT is recommended for severe depression when other tx methods have failed. The routine use of ECT for moderate depression is not recommended, unless depression has not responded to multiple drug and psychological tx. rTMS should be reserved for research purposes only because of uncertainty about clinical efficacy.</td>
<td>7</td>
</tr>
<tr>
<td>VA/DoD (2009)</td>
<td>Pts who do not respond to pharmacotherapy w/ a single agent may receive combination tx w/ pharmacotherapy and CBT or IPT. Pts who have not responded to 2 first-line ADs should either be switched to a new AD from a different class (venlafaxine is recommended, if not already tried) or receive augmentation w/ either medications or psychotherapy. Pts who have not responded to 3 different ADs should either receive augmentation with medications or psychotherapy or receive combination AD tx or ECT. Response/remission should be assessed at 8-12 wks after initiation of each new strategy. Significant response defined as 5-point reduction or score &lt;10 on PHQ-9 or ≤25% reduction in score on an accepted standardized instrument. Remission defined as PHQ-9 ≤4, BDI ≤10, or HAM-D ≤7, maintained for ≥1 month.</td>
<td>6 (literature search only through December 2006; procedure for updating guideline NR)</td>
</tr>
</tbody>
</table>

*According to the Rigor of Development domain of the Appraisal of Guidelines Research and Evaluation (AGREE) tool, along with a consideration of commercial funding and conflicts of interest among the guideline authors. Guidelines were scored on scale of 1 to 7 and judged to be good (6-7), fair (4-5), or poor (1-3).
HEALTH TECHNOLOGY EVIDENCE IDENTIFICATION

Discussion Document: What are the key factors and health outcomes and what evidence is there?

<table>
<thead>
<tr>
<th>Safety Outcomes</th>
<th>Safety Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive decline/effects</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td></td>
</tr>
<tr>
<td>Local effects (e.g., pain, itching)</td>
<td></td>
</tr>
<tr>
<td>Treatment emergent mania</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Efficacy – Effectiveness Outcomes</th>
<th>Efficacy / Effectiveness Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression relief</td>
<td></td>
</tr>
<tr>
<td>Relapse rates</td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td></td>
</tr>
<tr>
<td>Durability of benefit</td>
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<td>Quality of Life/Function</td>
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<tr>
<th>Special Population / Considerations Outcomes</th>
<th>Special Population Evidence</th>
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<tbody>
<tr>
<td>Unipolar vs bipolar MDD</td>
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<tr>
<td>TRD confirmed vs lack of well documented failure</td>
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<tr>
<td>Psychosis/retardation/agitation</td>
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<tr>
<td>Age</td>
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<tr>
<td>Race</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Disease severity</td>
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<td>Disease duration</td>
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<td>Symptom type</td>
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<tr>
<td>Comorbidities</td>
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<td>History of prior treatment</td>
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<thead>
<tr>
<th>Cost</th>
<th>Cost Evidence</th>
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<tr>
<th>Cost effectiveness</th>
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<td>ICER</td>
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Clinical Committee Evidence Votes

First Voting Question
The HTCC has reviewed and considered the technology assessment and information provided by the administrator, reports and/or testimony from an advisory group, and submissions or comments from the public. The committee has given greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Is there sufficient evidence under some or all situations that the technology is:

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<tr>
<th></th>
<th>Unproven (no)</th>
<th>Equivalent (yes)</th>
<th>Less (yes)</th>
<th>More (yes)</th>
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<tbody>
<tr>
<td>Effective</td>
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<td>Safe</td>
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<td>Cost-effective</td>
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Discussion
Based on the evidence vote, the committee may be ready to take a vote on coverage or further discussion may be warranted to understand the differences of opinions or to discuss the implications of the vote on a final coverage decision.

- Evidence is insufficient to make a conclusion about whether the health technology is safe, efficacious, and cost-effective;
- Evidence is sufficient to conclude that the health technology is unsafe, ineffectual, or not cost-effective;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for all indicated conditions;
- Evidence is sufficient to conclude that the health technology is safe, efficacious, and cost-effective for some conditions or in some situations.

A straw vote may be taken to determine whether, and in what area, further discussion is necessary.

Second Vote
Based on the evidence about the technologies’ safety, efficacy, and cost-effectiveness, it is

___ Not Covered    ___ Covered Unconditionally    ___ Covered under Certain Conditions

Discussion Item
Is the determination consistent with identified Medicare decisions and expert guidelines, and if not, what evidence is relied upon?
Clinical Committee Findings and Decisions

**Next Step: Cover or No Cover**
If not covered, or covered unconditionally, the Chair will instruct staff to write a proposed findings and decision document for review and final adoption at the following meeting.

**Next Step: Cover with Conditions**
If covered with conditions, the Committee will continue discussion.

1) Does the committee have enough information to identify conditions or criteria?
   - Refer to evidence identification document and discussion.
   - Chair will facilitate discussion, and if enough members agree, conditions and/or criteria will be identified and listed.
   - Chair will instruct staff to write a proposed findings and decision document for review and final adoption at next meeting.

2) If not enough or appropriate information, then Chair will facilitate a discussion on the following:
   - What are the known conditions/criteria and evidence state
   - What issues need to be addressed and evidence state

The chair will delegate investigation and return to group based on information and issues identified. Information known but not available or assembled can be gathered by staff; additional clinical questions may need further research by evidence center or may need ad hoc advisory group; information on agency utilization, similar coverage decisions may need agency or other health plan input; information on current practice in community or beneficiary preference may need further public input. Delegation should include specific instructions on the task, assignment or issue; include a time frame; provide direction on membership or input if a group is to be convened.

**Efficacy Considerations:**
- What is the evidence that use of the technology results in more beneficial, important health outcomes? Consider:
  - Direct outcome or surrogate measure
  - Short term or long term effect
  - Magnitude of effect
  - Impact on pain, functional restoration, quality of life
  - Disease management
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to no treatment or placebo treatment?
- What is the evidence confirming that use of the technology results in a more beneficial outcome, compared to alternative treatment?
- What is the evidence of the magnitude of the benefit or the incremental value
- Does the scientific evidence confirm that use of the technology can effectively replace other technologies or is this additive?
- For diagnostic tests, what is the evidence of a diagnostic tests’ accuracy
  - Does the use of the technology more accurately identify both those with the condition being evaluated and those without the condition being evaluated?
- Does the use of the technology result in better sensitivity and better specificity?
- Is there a tradeoff in sensitivity and specificity that on balance the diagnostic technology is thought to be more accurate than current diagnostic testing?
- Does use of the test change treatment choices

**Safety**
- What is the evidence of the effect of using the technology on significant morbidity?
  - Frequent adverse effect on health, but unlikely to result in lasting harm or be life-threatening, or;
  - Adverse effect on health that can result in lasting harm or can be life-threatening.
- Other morbidity concerns
- Short term or direct complication versus long term complications
- What is the evidence of using the technology on mortality – does it result in fewer adverse non-fatal outcomes?

**Cost Impact**
- Do the cost analyses show that use of the new technology will result in costs that are greater, equivalent or lower than management without use of the technology?

**Overall**
- What is the evidence about alternatives and comparisons to the alternatives
- Does scientific evidence confirm that use of the technology results in better health outcomes than management without use of the technology?