Washington State Health Care Authority
Health Technology Assessment

Order of Scheduled Presentations

***TOPIC*:** Treatment-resistant Depression

	Name	Notes
1.	John Neumaier, MD, PhD	No slides.
2.	Anna Borisovskaya, MD	No slides.
3.	Farrokh Farrokhi, MD Vice President, WA State Association of Neurological Surgeons	
4.	Mercy Yule, EAMP	

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		x
2.	Equity interests such as stocks, stock options or other ownership interests.		x
3.	Status or position as an officer, board member, trustee, owner.		x
4.	Loan or intellectual property rights.		x
5.	Research funding.		x
6.	Any other relationship, including travel arrangements.		x

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

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		x

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 [redacted] Feb 20, 2014 John F Neumaier, MD, PhD

Signature *Date* *Print Name*

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

Washington State Health Care Authority

Health Technology Assessment

Disclosure

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.	✓	
2.	Equity interests such as stocks, stock options or other ownership interests.		✓
3.	Status or position as an officer, board member, trustee, owner.		✓
4.	Loan or intellectual property rights.		✓
5.	Research funding.		✓
6.	Any other relationship, including travel arrangements.		✓

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

VAMC, Puget Sound - I work there. VA has no stakeholder interest in the products or treatments I will be discussing.

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		✓

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X [redacted] 02/21/14 [redacted], MD

Signature Date Print Name

For questions contact: Christine Masters
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360-725-5126

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2.	Equity interests such as stocks, stock options or other ownership interests.		✓
3.	Status or position as an officer, board member, trustee, owner.		✓
4.	Loan or intellectual property rights.		✓
5.	Research funding.		✓
6.	Any other relationship, including travel arrangements.		✓

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

_____

_____

_____

	Potential Conflict Type	Yes	No
7.	Representation: if representing a person or organization, include the name and funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).		✓

If yes to #7, provide name and funding Sources: _____

_____

_____

_____

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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 [redacted] 2/27/14 Elizabeth Fenwick

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

PRIORITY COMMUNICATION

Subcallosal Cingulate Gyrus Deep Brain Stimulation for Treatment-Resistant Depression

Andres M. Lozano, Helen S. Mayberg, Peter Giacobbe, Clement Hamani, R. Cameron Craddock, and Sydney H. Kennedy

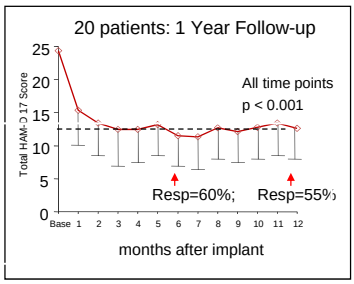
2008

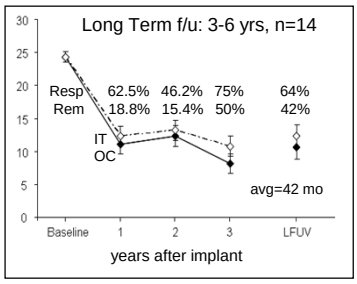
AJP in Advance. Published February 1, 2011 (doi: 10.1176/appi.ajp.2010.10081187)

Article

Deep Brain Stimulation for Treatment-Resistant Depression: Follow-Up After 3 to 6 Years

2011





Emory Studies: Replication, Extension

Arch Gen Psychiatry. 2012;69(2):150-158. doi:10.1001/archgenpsychiatry.2011.1456

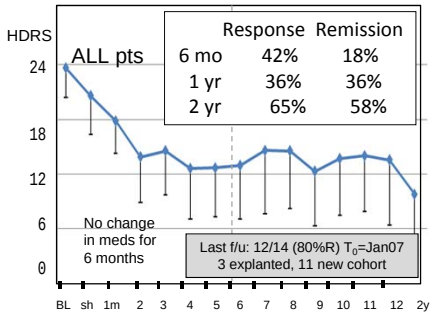
Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Unipolar and Bipolar Depression

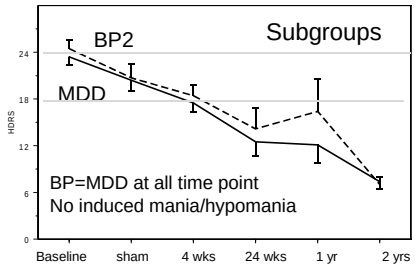
Paul E. Holtzheimer, MD; Mary E. Kelley, PhD; Robert E. Gross, MD, PhD; Megan M. Filkowski, BA; Steven J. Garlow, MD, PhD; Andrea Barrocas, MA; Dylan Wint, MD; Margaret C. Craighead, BA; Julie Kozarsky, BA; Ronald Chismar, RN; Jared L. Moreines, BS; Klaus Mewes, PhD; Patricio Riva Posse, MD; David A. Gutman, MD, PhD; Helen S. Mayberg, MD

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

- 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)



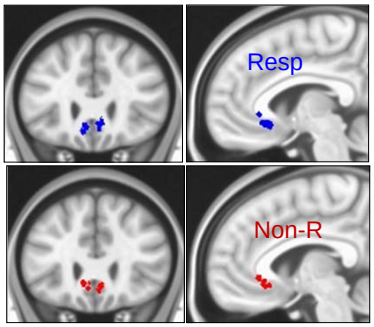


Funding: Dana, Stanley, Woodruff Found'n , Emory Hosp
Devices donated by St. Jude Medical , IDE: G060028/S002

One Source of Response Variability

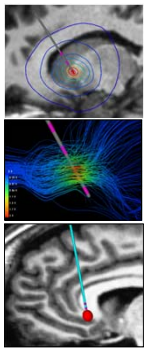
surgical precision

Location of Active Contacts



Standardized to AC-PC mean MNI space

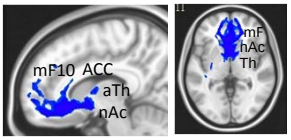
Voltage Field Modeling (TAM)



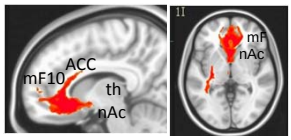
Butson & McIntyre Brain Stim 2008

TAM-seed Probablistic Tractography

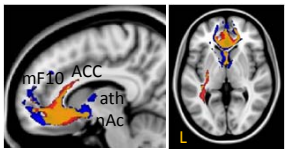
6m R N=6



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

Any unmarked topic will be considered a "Yes"

	Potential Conflict Type	Yes	No
1.	Salary or payments such as consulting fees or honoraria in excess of $10,000.		X
2.	Equity interests such as stocks, stock options or other ownership interests.		X
3.	Status or position as an officer, board member, trustee, owner.		X
4.	Loan or intellectual property rights.		X
5.	Research funding.		X
6.	Any other relationship, including travel arrangements.		X

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Ø

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Ø

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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 [redacted] 2/28/2014 MERCY YULE, EMP

Signature *Date* *Print Name*

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.

[redacted] 2/28/2014

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.

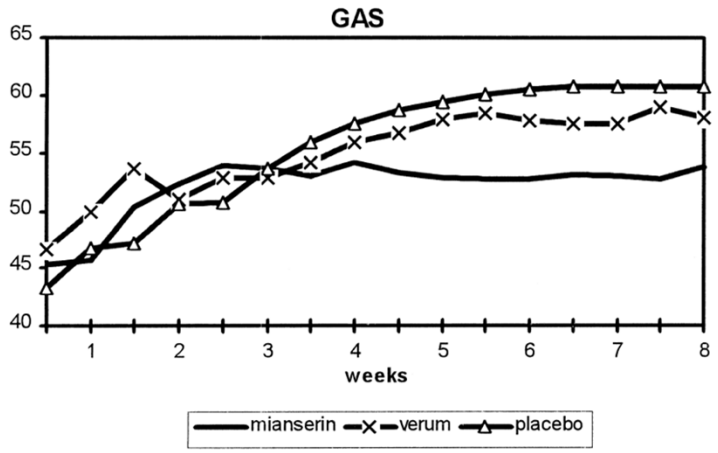
Studies: Acupuncture for MDD

- Roschke, J., et al (2000). The benefit from whole body acupuncture in major depressive disorder. Journal of Affective Disorders. 57: 73-81
- Qu, Shan-shan, et al (2013). A 6-week randomized controlled trial with a 4-week follow-up of acupuncture combined with paroxetine in patients with major depressive disorder. Journal of Psychiatric Research. 47: 726-732
- Song, C., Halbreich, U., Leonard, B., Luo, H. (2009). Imbalance between pro- and anti-inflammatory cytokines, and between Th1 and Th2 cytokines in depressed patients: The effect of electroacupuncture or fluoxetine treatment. Pharmacopsychiatry. 42: 182-188
- Zhang, Z., et al (2010) The effectiveness and safety of acupuncture therapy in depressive disorders: Systematic review and meta-analysis. Journal of Affective Disorders. 124 : 9-21

Whole body acupuncture for major depressive disorder

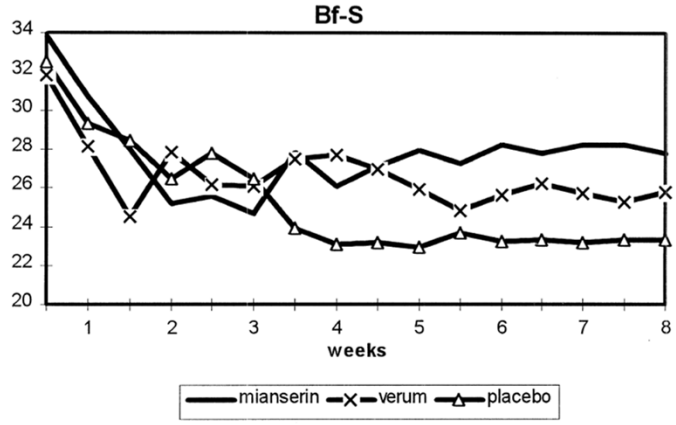
- Single-blind placebo controlled study of 70 inpatients with major depressive disorder divided into three groups:
- Specific standardized acupuncture points
- Non-specific acupuncture points
- Pharmacological management
- Treatments were given for a period of 4 weeks
- Patients were evaluated 2 times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

Whole body acupuncture for major depressive disorder



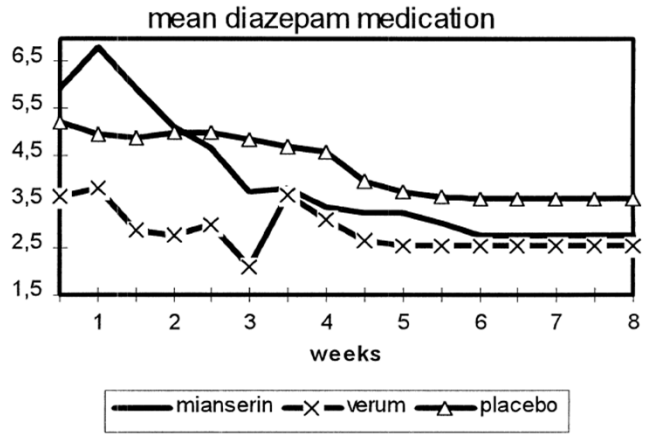
GAS ratings (global assessment) over time (the better the score, the better the psychopathology).

Whole body acupuncture for major depressive disorder

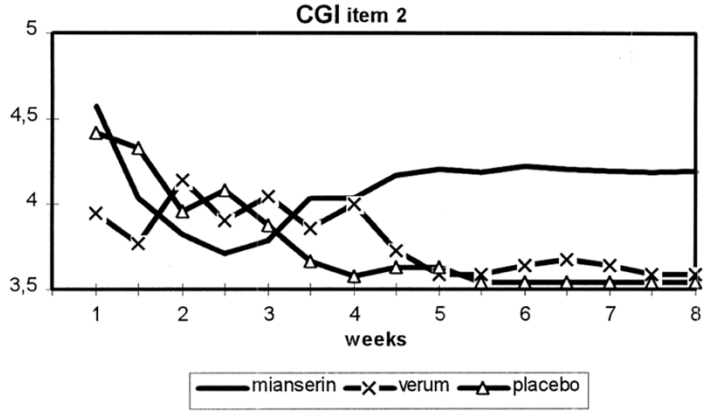


Bf-S self ratings (depressive mood) over time (the lower the score, the better the psychopathology).

Whole body acupuncture for major depressive disorder

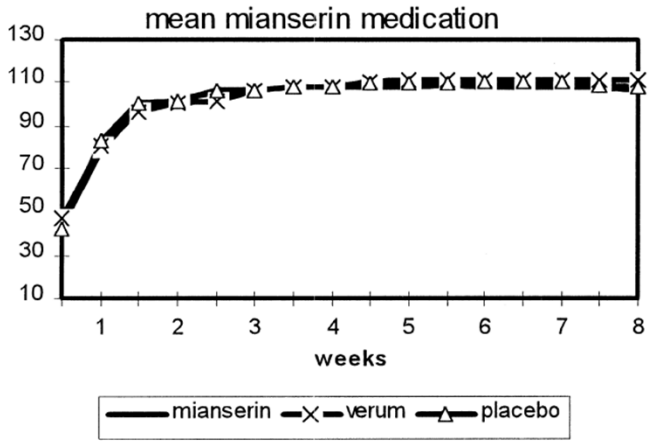


Whole body acupuncture for major depressive disorder



CGI ratings (item 2 = improvement) over time (the lower the score, the better the psychopathology).

Whole body acupuncture for major depressive disorder



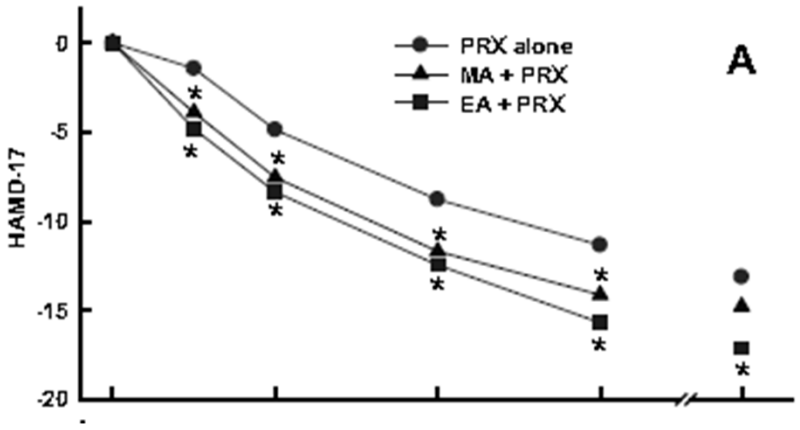
Whole body acupuncture for major depressive disorder

- Conclusion: " Acupuncture did improve the course of depression more than pharmacological treatment…"

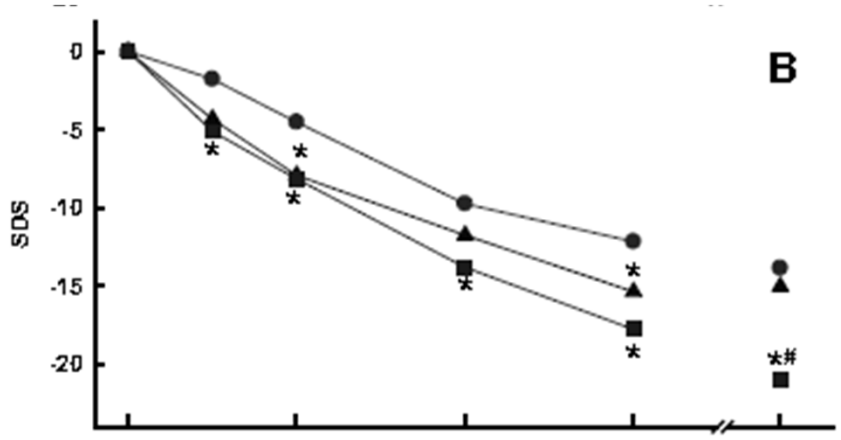
Acupuncture combined with paroxetine for MDD

- 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



Acupuncture combined with paroxetine for MDD



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…"

Cytokines and depression: The effect of electroacupuncture

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

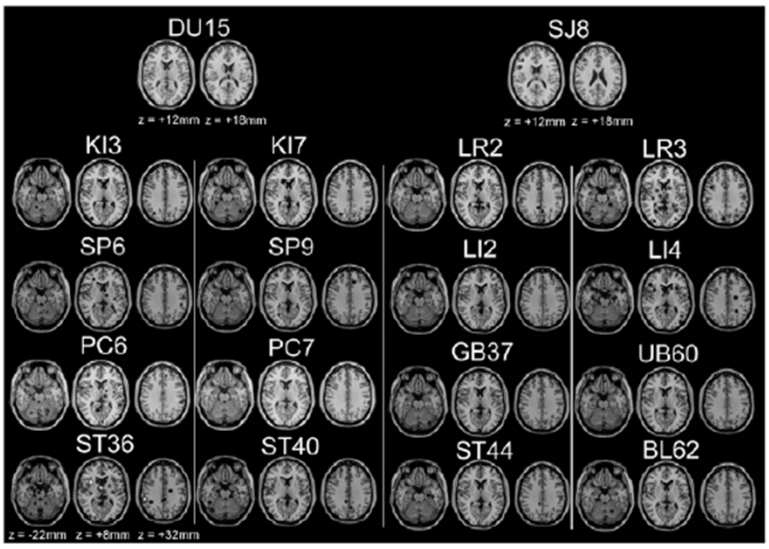
Cytokines and depression: The effect of electroacupuncture

- 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

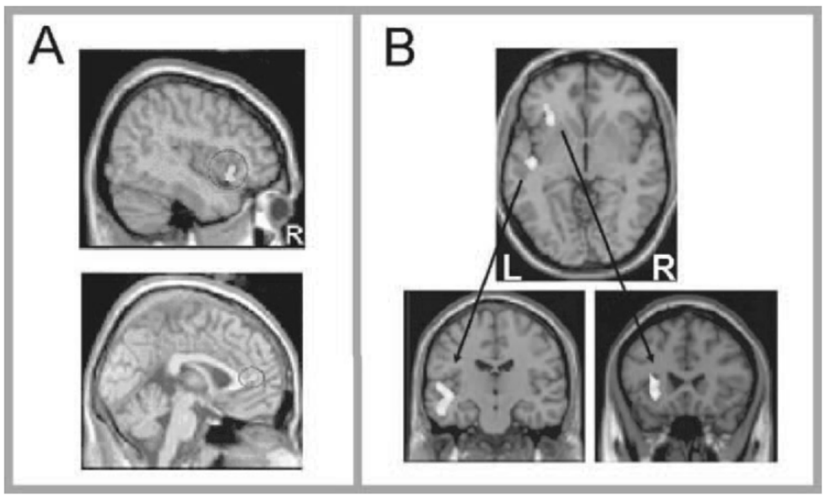
Cytokines and depression: The effect of electroacupuncture

- 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



Neural Imaging: Dhond, 2007



Systematic review: Acupuncture for depressive disorders

- 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.

Washington State Health Care Authority
Health Technology Assessment

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

Washington State Health Care Authority

Health Technology Assessment

Disclosure

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3.	Status or position as an officer, board member, trustee, owner.		✓
4.	Loan or intellectual property rights.		✓
5.	Research funding.		✓
6.	Any other relationship, including travel arrangements.	✓	

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

Cervel Neurotech Inc - Data Safety Monitoring Board - $1,500 per year - This company makes TMS machines. Clinically I administer Electro convulsive therapy.

	Potential Conflict Type	Yes	No
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X [redacted] 2/23/14 David H. Avery

Signature *Date* *Print Name*

For questions contact: Christine Masters
Health Technology Assessment
PO Box 42712
Olympia, WA 98504-2712
360-725-5126 FAX 360-586-8827

February, 2014

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 AFFLIATION:

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, Shijiazhaung, 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 Temperature Rhythms in Depression." 1981-1982, $5,358.

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.

Graduate School Research Fund Grant "Thermoregulation and Circadian Rhythms in Seasonal Affective Disorder." 1988-1989, $7,500.

Alcohol and Drug Abuse Institute, "Dawn Simulation Treatment of Abstinent Alcoholics with Winter Depression." April 1, 1993 to March 31, 1995, $14,985.

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.

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l8. Dunner, D.L., Ishiki, D., Avery, D.H., Wilson, L.G. and Hyde, T.S.: Effect of alprazolam and diazepam on anxiety and panic attacks in panic disorder: A Controlled study. J. Clin. Psych. 47:458-460, l986.

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62. Holtzheimer PE, Avery DH. Focal brain stimulation for treatment-resistant depression: transcranial magnetic stimulation, vagus-nerve stimulation, and deep-brain stimulation. Primary Psychiatry, 12 (2):57-64, 2005.
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CHAPTERS:

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1. Avery, D.: "The case for "shock" therapy." Psychology Today, p. 104, 1977.

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Abstracts (First-Author)

Regional Meetings:

"Morning versus Evening Light in the Treatment of Winter Depression" West Coast College of Biological Psychiatry, San Diego, March 28, 1987.

"Morning versus Evening Bright Light in the Treatment of Winter Depression: A Replication." West Coast College of Biological Psychiatry, Seattle, April 15, 1988.

"Circadian Temperature Rhythms in Winter Depression During a Constant Routine" West Coast College of Biological Psychiatry, Mt. Hood, February 25, 1989.

"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.

"Transcranial Magnetic Stimulation in the Treatment of Major Depression" West Coast College of Biological Psychiatry. Seattle, June 21, 1997.

"Transcranial Magnetic Stimulation in the Treatment of Major Depression." West Coast College of Biological Psychiatry. Tucson, Arizona, April 9, 1999.

"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.

"Transcranial Magnetic Stimulation in the Treatment of Major Depression: A Preliminary Analysis" West Coast College of Biological Psychiatry, Seattle, April 5, 2003.

"Transcranial Magnetic Stimulation in the Treatment of Major Depression." West Coast College of Biological Psychiatry, Los Angeles, March 13, 2004.

"Seasonal Affective Disorder" Psychiatry Update, Seattle, February 3, 2005.

"Transcranial Magnetic Stimulation in Psychiatry" Oregon Psychiatric Association Meeting, Ashland, Oregon, September 17, 2005.

"Treating Sleep Disorders in the Psychiatric Patient" Western State Hospital, Ft. Steilacoom, WA, February 23, 2006.

"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

"Transcranial Magnetic Stimulation in Psychiatry" Washington State Psychiatric Association Meeting, Seattle, WA, 3/15/2008

"Transcranial Magnetic Stimulation in Psychiatry: Current Status and Future Directions" Grand Rounds, University of Washington Department of Psychiatry and Behavioral Sciences, Seattle, WA, November 19, 2010.

"Transcranial Magnetic Stimulation in Psychiatry: Current Status and Future Directions" King Country Medical Society, Seattle, WA, May 10, 2011.

National

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

"Nocturnal Temperature in Affective Disorder" Society of Biological Psychiatry, New Orleans, May, 1981.

"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.

"Nocturnal Temperature Discomfort and Night Sweats in Primary Depression and Insomnia" Sleep Research 13:33, 1984.

"Winter Depression and Response to A.M. and P.M. Light" American Psychiatric Association Symposium concerning Treatment of Winter Depression with Light. Montreal, May 9, 1988.

"The Temperature Rhythm is Phase-Delayed in Winter Depression" Meeting of the Society of Biological Psychiatry, San Francisco, May 5, 1989.

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

"Phase Typing Seasonal Affective Disorder Using a Constant Routine" Association of Professional Sleep Societies, Washington DC. June 24, 1989.

"Sleep and Circadian Temperature Rhythms in Winter Depression" 11th Annual international Conference of the IEEE Engineering in Medicine and Biology Society, November 9, 1989.

"The Temperature Rhythm is Phase-Delayed in Winter Depression" Meeting of the Society of Biological Psychiatry New York, May 11, 1990.

"Is Dawn Simulation Effective in Treating Winter Depression?" Meeting of the Society for Light Treatment and Biological Rhythms, New York May 13, 1990.

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

"Is the Temperature Setpoint Elevated in Depression?" Meeting of the Society of Biological Psychiatry, May 11, 1991.

"Dawn Simulation Treatment for Winter Depression: A Controlled Study." Society for Light Treatment and Biological Rhythms, Toronto, Jun 13, 1991.

"Does an Elevated Temperature Setpoint Explain the REM and SWS Abnormalities of Depression?" Meeting of the Association of Professional Sleep Societies. Toronto, June 16, 1991.

"Dawn Simulation Treatment of Winter Depression: A Second Controlled Study." Meeting of the Society for Light Therapy and Biological Rhythms, Bethesda, April 30, 1992.

"Dawn Simulation Treatment of Winter Depression" Association of Professional Sleep Societies, Phoenix, June 2, 1992.

"Dawn Simulation Treatment of Winter Depression: A Second Controlled Study" Meeting of the Society of Biological Psychiatry, San Francisco, May 21, 1993.

"Is PSI E-M Increased in Winter Depression?" Society for Light Treatment and Biological Rhythms, San Diego, June 19, 1993.

"Is the Low Temperature Trough Duration Increased During a Constant Routine in Winter Depression?" Meeting of the Association of Professional Sleep Societies, Los Angeles, June 23, 1993. Sleep Research 22: 392, 1993.

"Is PSI E-M Increased in Winter Depression?" Meeting of Society of Biological Psychiatry. Philadelphia, May 20, 1994. Biological Psychiatry 1994;35:668.

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

"A Seasonal and Circadian Study of Suicide over a 10-year period in the Seattle Area" Meeting of the Society of Biological Psychiatry. Miami, May 18, 1995.

"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.

"The Morningness-Eveningness Questionnaire in SAD in the Summer, Winter, and After Light Treatment." Meeting of the Society of Light Treatment and Biological Rhythms, Vancouver, British Columbia, June 7, 1997.

"Nocturnal Sweating in Depression" Meeting of the Society of Light Treatment and Biological Rhythms, Amelia Island, Florida, May 8, 1998.

"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.

"An Association between REM Latency and Nocturnal Temperature in Depression. Fourth International Congress of Sleep Research, Bologna, Italy, 1983.

"Nocturnal Temperature Discomfort and Night Sweats in Primary Depression and Insomnia" 24th Annual Sleep Research Society Meeting, Toronto, Canada, June, 1984.

"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.

"Resynchronization of the Temperature Rhythm in a Catatonic Patient Treated with ECT" 5th International Congress of Sleep Research, Copenhagen, Denmark, June, 1987. Sleep Research 16:285, 1987.

"Bright Light Treatment of SAD: AM versus PM Light" as part of the World Psychiatric Association Regional Symposium "New Developments in SAD and Phototherapy", Washington DC, October 15, 1988.

"Dawn Simulation Treatment of Winter Depression" XIXth Collegium Internationale Neuro-Psychopharmacologium Congress, Washington, D.C. June 28, 1994.

"Is PSI E-M Increased in Winter Depression?" Meeting of the International Society of Psychoneuroendocrinology, Seattle, August 15, 1994.

"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.

"ISTS database for studies of transcranial magnetic stimulation in the treatment of depression." International Symposium on Transcranial Magnetic Stimulation. Goettingen, Germany, October 2, 1998. Electroencephalography and Clinical Neurophysiology 107 (3):93P, 1998.

"TMS in the Treatment of Medication-Free Major Depression" International Society of Transcranial Stimulation Meeting, Chicago, May 10, 2000.

" Repetitive Transcranial Magnetic Stimulation (rTMS) is Clinically Effective in Medication-Resistant Major Depression" XXIV Collegium Internationale Neuro-Psychopharmacologium Congress, Paris, June 24, 2004

"The Basics of Transcranial Magnetic Stimulation" World Federation of Societies of Biological Psychiatry Meeting, Vienna, Austria July 2, 2005.

"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 Treatment-Resistant Depression" Danish University Antidepressant Group. Fredensborg, Denmark, November 7, 2008.

"TMS in the Treatment of Chronic Pain" EEG and Clinical Neuroscience Meeting, Keynote Lecture, Istanbul, Turkey, September 16, 2010.

"TMS in Treatment of Medication Resistant Major Depressive Disorder" EEG and Clinical Neuroscience Meeting, Istanbul, Turkey, September 16, 2010.

"Is Combining Non-invasive Brain Stimulation (TMS) with Non-invasive Brain Imaging (fMRI) – interleaved TMS/fMRI – the Ultimate in Multimodal Imaging or a Mere Distraction?" EEG and Clinical Neuroscience Meeting, Istanbul, Turkey, September 16, 2010.

"Transcranial Magnetic Stimulation and Pulsed Electromagnetic Field Therapy in Treatment-Resistant Depression" Danish University Antidepressant Group. Nyborg, Denmark, November 7, 2010.

Selected abstracts of collaborators who were first authors:

Smallwood RG, Avery DH, Pascualy RA, and Prinz PN: "Circadian Temperature Rhythms in Primary Depression" Sleep Research 12:215, 1983.

Dager SR, Cowley D, Avery D, Elder J, Roy-Byrne P, Dunner D: "Clinical Characteristics of Placebo Response Among Panic Patients" American College of Neuropsychopharmacolgy, December, 1989.

Dahl K, Avery D, Savage M, Brengelmann G, Kenny M, Lewy A, Larsen L, Vitiello M, and Prinz P: "Temperature, Melatonin and TSH in Seasonal Affective Disorder During a Constant Routine" Society of Light Therapy and Biological Rhythms, New York, May, 1990.

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.

Norden MJ, Avery DH: "A Controlled Study of Dawn Simulation in Subsyndromal Seasonal Affective Disorder" Society of Light Treatment and Biological Rhythms, Bethesda, May, 1992.

Brengelmann GL, Savage MV, Avery DH: "Reproducibility of Sweat Rate Thresholds" FASEB, Anaheim, CA, April, 1992.

Eder DN, Vitiello MV, Avery DH and Smith JR. (1992) The temporal covariation of delta EEG and body temperature during sleep. Sleep Research (22). Paper presented at the American Professional Sleep Society Meeting, LA, June 1993.

Eder DN, Avery DH, Dahl K: "Estimation of Human Circadian Phase from Body Temperature Using Waveform Feature Extraction" 11th European Congress on Sleep Research, Helsinki, Finland, July 1992.

Norden M, Avery D: "Association of Alcohol Consumption and Ambient Temperature: Implications for Serotonin Function and Thermoregulation." Society of Biological Psychiatry meeting, San Francisco, May, 1993.

Norden M, Avery D: "Heat and Violence Correlate Independent of Season" American Psychiatric Association, San Francisco, May, 1993.

Eder DN, Avery D: "Sleep Architecture in Symptomatic SAD and Changes Following Dawn Simulation: A Naturalistic Study." Meeting of the Society for Light Therapy and Biological Rhythms, San Diego, June 20, 1993.

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, Vitiello MV and Avery DH: "Links between delta EEG intensity and thermoregulatory drive." Meeting of the Society of Biological Psychiatry, Philadelphia, May 1994.

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, Vitiello MV and Avery DH. "Evidence of the role of delta-EEG intensity in mediating core temperature cooling." Invited speaker at the Young Scientists Symposium of the 12th Congress of the European Sleep Research Society, Florence, May 1994 and presented at the 9th Annual Meeting of the Association of Professional Sleep Societies, Boston, June 1994.

Eder DN, Avery DH, and Wildschiødtz G. "Sleeping in Seattle: Seasonal variation in sleep measures." J. Sleep Res. 5(suppl. 1):56, 1996.

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.

Derek N. Eder, David H. Avery, Gordon Wildschiødtz, Henrik Dam, Tom G. Bolwig: "SAD, asleep and unresponsive: Sleep regulation in Seasonal Affective Disorder" Meeting of the Society of Light Therapy and Biological Rhythms, Amelia Island, Florida, May 8, 1998.

P.S. Ciechanowski, D.N. Eder, W.J. Katon, D.H. Avery. Correlation of Solar Radiation and Glycosylated Hemoglobin Levels in Patients with Diabetes. Chronobiology International.2002, vol.19, no. 5, 964-965.

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", Lillihagen Hospital, Goteborg, Sweden, May, 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.

"Circadian Rhythm Abnormalities in Depression, University of British Columbia, February 12, 1988.

"Bright Light Treatment of Winter Depression", University of British Columbia, February 12, 1988.

“Dawn Simulation Treatment of Seasonal Affective Disorder” Meeting of the Association of Professional Sleep Societies, Los Angeles June 23, 1993.

"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" Commonwealth Club, San Francisco, October 14, 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.

Co-Leader of Workshop, "Transcranial Magnetic Stimulation (TMS): Technique and Demonstration" Meeting of the Society of Biological Psychiatry, San Diego, May 17, 1997.

"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.

"Transcranial Magnetic Stimulation Treatment of Depression" Central Neuropsychiatric Association 1999 Scientific Program, Los Angeles, October 15, 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 the Treatment of Medication-Resistant Depression", Psychiatry Update, Seattle, Nov. 18, 1999.

"Psychopharmacology of Aggression" Psychiatry Update, Seattle, Nov. 19, 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

"Management of Treatment-Resistant Depression: New Antidepressants and New Approaches in Light Therapy" Snoqualmie, WA June 11, 2000.

"Light Therapy in the Treatment of Winter Depression" Washington State Psychiatric Association, Wenatchee, WA, September 23, 2000.

"Transcranial Magnetic Stimulation in the Treatment of Depression" Washington State Psychiatric Association, Wenatchee, WA, September 23, 2000.

"Effects of Light on Mood and Human Behavior" Northwest Section of the Dark-Sky Association, University of Washington, Seattle, Dec. 2, 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.

"Transcranial Magnetic Stimulation in the Treatment of Depression" NCDEU Meeting, Phoenix, May 29, 2001.

“Transcranial Magnetic Stimulation in the Treatment of Depression” University of Louisville, Louisville, Kentucky, March 23, 2002.

“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.

“Recent Advances in the Treatment of Seasonal Affective Disorder.” University of Washington CME Course, Seattle, WA., December 13, 2002.

“Psychopharmacologic Management of Agitation” CME presentation at Providence St. Peters Hospital, Olympia, WA , January 16, 2003.

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

"Recent Advances in Transcranial Magnetic Stimulation in the Treatment of Depression" Grand Rounds, University of Illinois at Chicago, March 12, 2003.

"Transcranial Magnetic Stimulation in the Treatment of Major Depression." West Coast College of Biological Psychiatry, Seattle, WA, April 5, 2003.

"Assessment and Treatment of Sleep Disorders" Nursing CME Program, Shoreline, WA June 13, 2003.

"Transcranial Magnetic Stimulation in the Treatment of Major Depression" Tanta University, Tanta, Egypt, February 19, 2004.

"Light and Circadian Rhythm Abnormalities in Major Depression." Tanta University, Tanta, Egypt, February 19, 2004.

"Transcranial Magnetic Stimulation in the Treatment of Major Depression." West Coast College of Biological Psychiatry, Los Angeles, CA, March 13, 2004.

"Transcranial Magnetic Stimulation in the Treatment of Major Depression: A Review of the Meta-analyses." National Institute of Drug Abuse Workshop, *Transcranial Magnetic Stimulation in the Treatment of Drug Abuse and other Brain Disorders*, Bethesda, MD, March 16, 2004.

"Transcranial Magnetic Stimulation in the Treatment of Major Depression: A Review of the Meta-analyses." New Clinical Drug Evaluation Unit (NCDEU) Meeting, Phoenix, AZ, June 3, 2004.

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

"Transcranial Magnetic Stimulation Course" with Sarah H. Lisanby, M.D., EEG and Clinical Neuroscience Society (ECNS) Meeting, Irvine, CA, October 1, 2004.

"The Basic Principles of TMS" 8th World Congress of Biological Psychiatry. Vienna, July, 2005.

"Treatments for Medication-Resistant Depression": Transcranial Magnetic Stimulation and Vagus Nerve Stimulation." Oregon Health Sciences University, Portland, OR, February 28th, 2006.

"Recent Advances in the Treatment of Insomnia" Washington State Pharmacy Association, September 19, 2006.

"Transcranial Magnetic Stimulation in the Treatment of Depression" Grand Rounds, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, September 25, 2006.

"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: New Treatment for Depression" Advanced Practice in Primary and Acute Care 2007, University of Washington School of Nursing, Seattle, WA November 8, 2007.

"Transcranial Magnetic Stimulation in Psychiatry" Washington State Psychiatric Association Meeting, Seattle, WA, 3/15/2008

"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.

"Transcranial Magnetic Stimulation in Treatment-Resistant Depression" Danish University Antidepressant Group. Fredensborg, Denmark, November 7, 2008.

"TMS in the Treatment of Chronic Pain" EEG and Clinical Neuroscience Meeting, Keynote Lecture, Istanbul, Turkey, September 16, 2010.

"TMS in Treatment of Medication Resistant Major Depressive Disorder" EEG and Clinical Neuroscience Meeting, Istanbul, Turkey, September 16, 2010.

"Is Combining Non-invasive Brain Stimulation (TMS) with Non-invasive Brain Imaging (fMRI) – interleaved TMS/fMRI – the Ultimate in Multimodal Imaging or a Mere Distraction?" EEG and Clinical Neuroscience Meeting, Istanbul, Turkey, September 16, 2010.

"Transcranial Magnetic Stimulation and Pulsed Electromagnetic Field Therapy in Treatment-Resistant Depression" Danish University Antidepressant Group. Nyborg, Denmark, November 7, 2010.

"Transcranial Magnetic Stimulation in Psychiatry: Current Status and Future Directions" Grand Rounds, University of Washington Department of Psychiatry and Behavioral Sciences, Seattle, WA, November 19, 2010.

"Transcranial Magnetic Stimulation in Psychiatry: Current Status and Future Directions" King Country Medical Society, Seattle, WA, May 10, 2011.

Washington State Health Care Authority

Agency Medical Director Comments

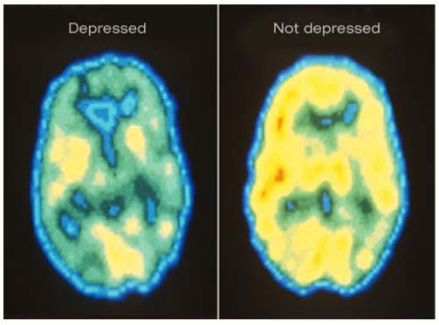
Non-Pharmacologic Therapies for Treatment Resistant Depression

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

Background

Treatment Resistant Depression (TRD)

- 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



http://www.nimh.nih.gov/statistics/1mdd_adult.shtml

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Background

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

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Background

Treatment Resistant Depression (TRD) Setting the Stage

- **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".**

http://www.nimh.nih.gov/health/trials/practical/stard/backgroundstudy.shtml

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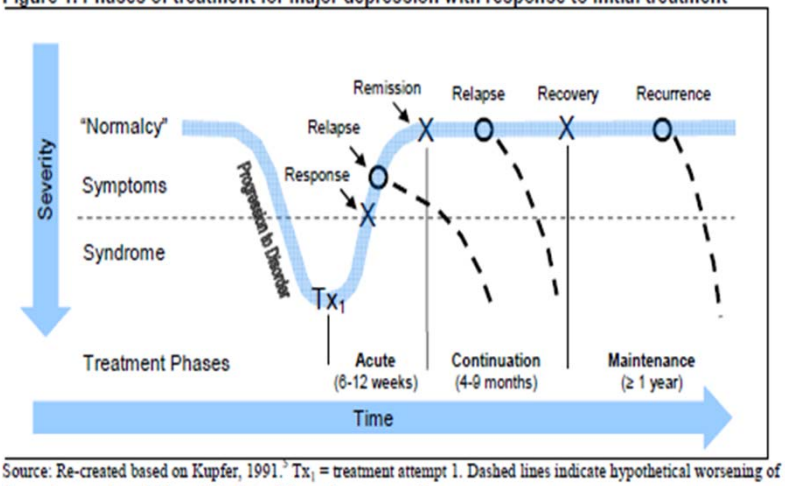
Background

Figure 1. Phases of treatment for major depression with response to initial treatment



Source: Re-created based on Kupfer, 1991.[2] Tx_1 = treatment attempt 1. Dashed lines indicate hypothetical worsening of depressive severity, which could indicate failure of treatment, relapse, or recurrence.

Gaynes BN, Lux L, Lloyd S, Hansen RA, et. Al. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Review. Agency for Healthcare Research and Quality. September 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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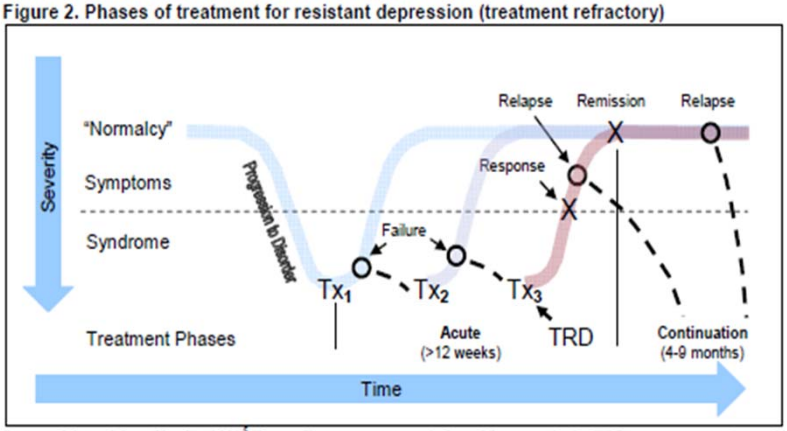
Background

Figure 2. Phases of treatment for resistant depression (treatment refractory)



Source: Adopted from Kupfer, 1991[2] Tx_{1-3} = Treatment attempt 1, 2, and 3, respectively; TRD = treatment-resistant depression. Dashed lines indicate hypothetical worsening of depressive severity, which could indicate failure of treatment, relapse, or recurrence.

Gaynes BN, Lux L, Lloyd S, Hansen RA, et. Al. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Review.Agency for Healthcare Research and Quality. September 2011.www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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Treatment Resistant Depression

Treatment Modalities

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

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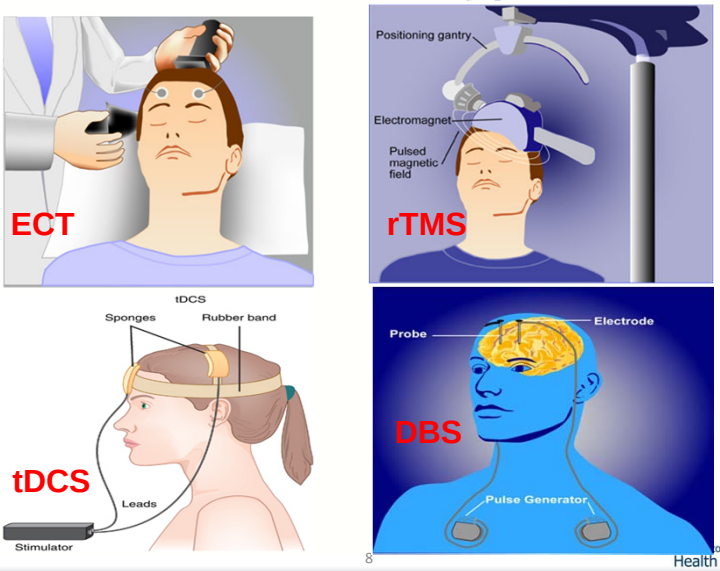
Treatment Resistant Depression

Treatment Types



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Treatment Resistant Depression

AMDG Perspective

Primary Criteria Ranking

- Safety = Medium
- Efficacy = High
- Cost = Medium

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Treatment Resistant Depression

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

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Washington State Health Care Authority

Treatment Resistant Depression

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

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Treatment Resistant Depression

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

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Washington State Health Care Authority

Treatment Resistant Depression:
State Agency Utilization

Electroconvulsive Therapy (ECT)

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

PEB/UMP and L&I – 100% episodic and depression diagnoses
Medicaid – 85% episodic & depression diagnoses. Other diagnoses: schizophrenia, psychosis

Treatment Resistant Depression:
State Agency Utilization

PEB/UMP ECT Top Diagnosis Codes n=72	Patients	% of All ECT Patients
RECUR DEPR PSYCH-SEVERE	38	52.8%
RECURR DEPR PSYCHOS-UNSP	31	43.1%
EPISODIC MOOD DISORD NOS	12	16.7%
BIPOL I SINGLE MANIC NOS	11	15.3%
DEPRESSIVE DISORDER NEC	11	15.3%
DEPRESS PSYCHOSIS-UNSPEC	10	13.9%
BIPOL I CURR DEP W/O PSY	8	11.1%
BIPOLAR DISORDER NEC	8	11.1%
BIPOL I CUR DEPRES NOS	7	9.7%
DEPRESS PSYCHOSIS-SEVERE	7	9.7%
REC DEPR PSYCH-PSYCHOTIC	7	9.7%

Treatment Resistant Depression: State Agency Utilization

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

State Agency Utilization

ECT Usage

PEB/UMP & Medicaid Procedure Counts, 2009-2012	2009	2010	2011	2012	4 Yr Overall Total
PEB/UMP Average Annual Members	**210,501**	**213,487**	**212,596**	**212,684**	
PEB Members w/Depression (Avg 9.2%)	19,475	19,922	19,581	19,425	
PEB/UMP ECT Patients (all with depression diagnoses)	**26**	**32**	**30**	**30**	**72**
Average Treatment Count per Patient	15.5	13.7	16.4	12.7	23.8
Max Treatment Count per Patient	48	48	62	49	205
PEB/UMP ECT Total Paid	**$298,744**	**$288,606**	**$384,272**	**$312,751**	**$1.3M**
Medicaid Fee for Service Population	**463,966**	**474,676**	**473,356**	**477,727**	
Medicaid Pts w/Depression (Avg 11.1%)	54,869	54,787	51,422	49,507	-4.30%
Medicaid ECT Patients (85% depression diagnoses)	**43**	**55**	**45**	**28**	**134**
Average Treatment Count per Patient	3.2	3.3	2.8	3.5	4.1
Max Treatment Count per Patient	8	9	10	10	22
Medicaid ECT Total Paid	**$26,017**	**$30,959**	**$14,574**	**$14,726**	**$86,275**

Treatment Resistant Depression:
State Agency Utilization

ECT Payments

Electroconvulsive Therapy, PEB/UMP and Medicaid Average Payments, 2009-2012	2009	2010	2011	2012	4 Yr Overall Total
PEB/UMP ECT Patients (all with depression diagnoses)	**26**	**32**	**30**	**30**	**72**
Average Treatment Count per Patient	15.5	13.7	16.4	12.7	23.8
PEB/UMP ECT Total Paid	**$298,744**	**$288,606**	**$384,272**	**$312,751**	**$1.3M**
Average Paid per Patient	$11,490	$9,019	$12,809	$10,425	$17,839
Average Paid per Patient, PEB Primary	$16,756	$10,891	$16,508	$15,548	$23,067
Medicaid ECT Patients (85% depression diagnoses)	**43**	**55**	**45**	**28**	**134**
Average Count per Patient	3.2	3.3	2.8	3.5	4.1
Medicaid ECT Total Paid	**$26,017**	**$30,959**	**$14,574**	**$14,726**	**$86,275**
Average Paid per Patient	$605	$563	$324	$526	$644
Average Paid per Patient, Non-Medicare[4]	$652	$686	$496	$925	$787

Treatment Resistant Depression:
State Agency Utilization

ECT Payments

Electroconvulsive Therapy, PEB/UMP and Medicaid Average Costs, 2009-2012	2009	2010	2011	2012	4 Yr Overall Total
PEB/UMP ECT Patients (all with depression diagnoses)	**26**	**32**	**30**	**30**	**72**
Average Treatment Count per Patient	15.5	13.7	16.4	12.7	23.8
PEB/UMP ECT Total Paid	**$298,744**	**$288,606**	**$384,272**	**$312,751**	**$1.3M**
Average Paid per Procedure	$739	$657	$779	$823	$748
Average Paid per Procedure, PEB Primary	$1,160	$1,122	$1,138	$1,503	$1,214
Medicaid ECT Patients (85% depression diagnoses)	**43**	**55**	**45**	**28**	**134**
Average Count per Patient	3.2	3.3	2.8	3.5	4.1
Medicaid ECT Total Paid	**$26,017**	**$30,959**	**$14,574**	**$14,726**	**$86,275**
Average Paid per Procedure	$191	$170	$114	$149	$158
Average Paid per Procedure, Non-Medicre	$215	$227	$231	$278	$230

Treatment Resistant Depression: State Agency Utilization

ECT

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

Treatment Resistant Depression: State Agency Utilization

Agency Allowed Patient Charges Breakdown: ECT Average Allowed $ per Patient	PEB/UMP Medicare	PEB/UMP Primary	Medicaid Medicare	Medicaid Non-Medicare Primary
Patient Count	n=21	n=44	n=43	n=85
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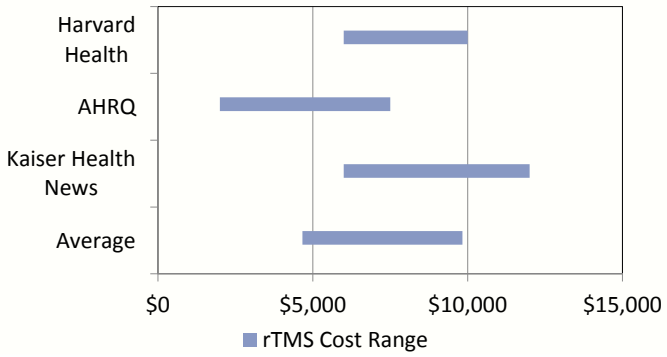
Total Average Allowed	**$35,479**	**$23,299**	**$1,396**	**$674**

Washington State Health Care Authority

2012 Published rTMS Treatment Cost Estimates



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

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Washington State Health Care Authority

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

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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

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Washington State Health Care Authority

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

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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 supports 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

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Questions?

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

Contact: shtap@hca.wa.gov

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Washington State Health Care Authority

Nonpharmacologic Treatments for Treatment-Resistant Depression

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

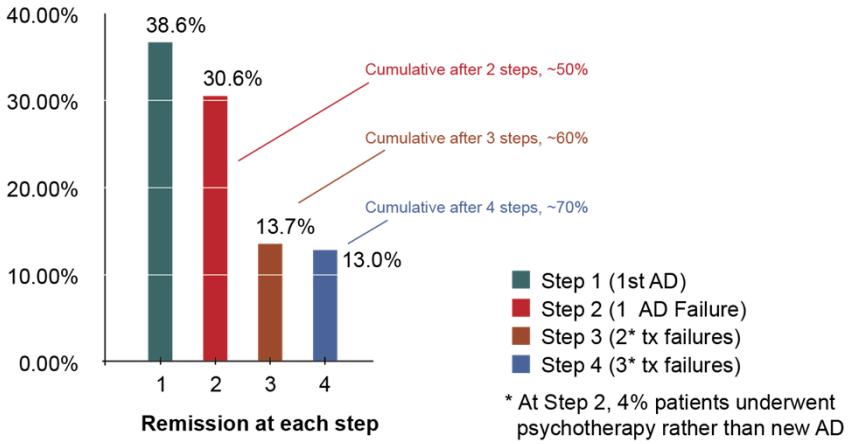
Abbreviations

- **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)



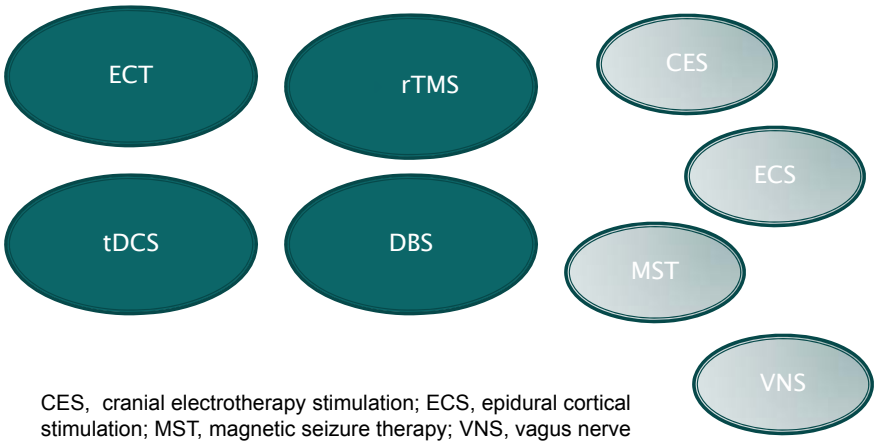
Background: TRD

- 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*



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

Background: Outcome measurement, depression

- Response: Typically, ≥50% reduction in depression score
- Remission: Score < specified cutoff
  - E.g., ≤8 on HAM-D_{17}, ≤10 on HAM-D_{21}, or ≤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 = partial response ≈ 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

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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

HAM-D / MADRS QOL

- 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

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Background: Technology descriptions

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

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Policy context

- Concern over safety, efficacy, and cost.
- Depression is relatively common and has effects on health, disability, and QOL.

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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).

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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?

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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, Embase, and PsycInfo
  - 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

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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)

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Search results

ECT	rTMS	tDCS	DB S
KQ #1a – Effectiveness			
4 RCTs (3 sham, 1 ECT vs pharmacotx)	1 SR/MA (AHRQ; pooled estimates, 24 RCTs [sham]) 3 RCTs (sham), post-AHRQ 1 ad hoc analysis 5 RCTs, rTMS vs ECT 2 RCTs, rTMS+ECT vs ECT	2 SRs/MAs (7 RCTs [sham] and 4 case series) 1 RCT (2 publications)	1 SR (Hayes 2012; no pooled estimates; 5 uncontrolled studies, 9 publications)
KQ #1b – Effectiveness by treatment parameter			
1 SR/MA 7 RCTs (comparator)	Data from 6 KQ #1a RCTs 4 RCTs (comparator)	Data from the KQ #1a SRs and RCT	---
KQ #2 – Safety			
Data from the KQ #1a and KQ #2b RCTs 2 SRs/MAs	Data from the KQ #1a and KQ #1b SR and RCTs 3 SRs/MAs	Data from the KQ #1a SRs and RCT 1 SR w/ safety-only data	Data from KQ #1a SR 3 SRs, safety-only data
KQ #3 – Differential effectiveness by patient characteristics			
2 SRs/MAs 1 post hoc analysis of 2 randomized comparator trials	Data from KQ #1a SR and RCTs	Data from KQ #1a SRs and RCT	Data from KQ #1a study
KQ #4 – Cost implications			
---	2 EEs, rTMS vs ECT 1 EE, rTMS vs pharmacology	---	---

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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

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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

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Findings: ECT

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ECT: KQ #1a (effectiveness)

Quantity/Quality, Studies	Quality, Body of Evidence	Direction of Findings	Magnitude of Benefit
Depression relief, vs sham 2 double-blind RCTs (sham); 1 RCT, ECT vs pharmacotx (fair all) 134 pts	**Low** Study weaknesses Small quantity data Uncertain applicability in 1 study	Favored ECT	***Difference in depression score change at end of tx:*** ~25 vs 18 points on HAM-D_{17} (0-54 scale) 15.6 vs 1.9 points on BDI (0-63 scale) 18.6 vs 9.6 on HAM-D_{21} (0-64 scale)
Suppl data (1 SR; 7 case series, 545 pts) (Heijnen et al., 2010)	---	---	*Pooled rate of remission: 48% (range 39%-63%)*
ECT vs rTMS	Discussed in next section	---	---
Vs tx as usual, psychotx, tDCS, DBS	**Insufficient** No data	---	---
Durability of effect, ECT vs sham	**Insufficient** 1 very small RCT	Compar-able, 6 mos	---
QOL/functional status	**Insufficient** No data	---	---
Maintenance tx w/ ECT+pharmacotx vs pharmacotx alone 1 unblinded RCT (fair) 56 pts	**Insufficient** Study weaknesses Extremely small quantity data	Favored ECT	***Relapse rates:*** 32% vs 61% (*P*=0.036); HR, 2.32 (CI, 1.03-5.22)

BDI, Beck Depression Inventory

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

Source	Change in Score Within Tx Arms	Response * Within Tx Arms	Remission* Within Tx Arms
STAR*D, Step 2 (1 AD failure) (Rush et al., 2006) 1475 pts	---	---	30.6%
STAR*D, Step 3 (2 AD failures) 622 pts; 2006	---	---	14.3%
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.)	Switch: 39.8% Augmentation:38.1% Maintenance: 27.3% (CI overlap)	Switch: 22.3% Augmentation: 27.2% Maintenance: 16.8% (CI overlap)
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)	---	---
Heijnen et al., 2010 SR, 7 case series, 545 pts; 1990-2008	---	---	48% (range 39%-63%)

*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)

Quantity/Quality, Studies	Quality, Body of Evidence	Direction of Findings	Magnitude of Benefit
Bifrontal stimulation Dunne et al., 2012 (good SR/MA; 8 double-blind RCTs, but no sham controls)	**Low** Lack of sham controls Inconsistency NS pooled effect sizes	Mixed	***Effect size:*** Bifrontal vs bitemporal: **0.102**, favoring bifrontal but NS (5 RCTs) Bifrontal vs unilateral: **–0.118** favoring unilateral but NS (7 RCTs)
Bilateral vs unilateral UK ECT Review Group, 2003 (fair SR/MA; 22 controlled trials)	**Moderate** Missing detail, study quality Uncertain applicability to population of interest	Favored bilateral	***Effect size:*** Fixed effects: **–0.323** (CI, –0.446 to –0.1.99) Random effects: **–0.322** (CI, –0.458 to –0.186)
High dose vs low dose UK ECT Review Group, 2003 (fair SR/MA; 6 controlled trials	**Moderate** Missing detail, study quality Uncertain applicability to population of interest	Favored high dose	***Effect size:*** Fixed effects: **0.571** (CI, 0.352–0.790) (favors higher dose) Random effects: **0.575** (CI, 0.329–0.829)

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ECT: KQ #1b (con't)

Quantity/Quality, Studies	Quality, Body of Evidence	Direction of Findings	Magnitude of Benefit
Frequency of sessions UK ECT Review Group, 2003 (fair SR/MA , 6 RCTs, 210 pts)	**Low** Missing detail, study quality Very small quantity of data NS findings	Favored 3x/wk over 1x/wk. Favored 2x/wk over 3x/wk but small NS effect.	**Results are presented as SES.** ***1x/wk vs 3x/wk (2 trials, 51 pts):*** Fixed effects: **0.841** (CI, 0.311 to 1.370) (favors 3x/wk) Random effects; **0.832 (**–0.389 to 1.890) ***2x/wk vs 3x/wk (SES) (4 trials, 159 pts):*** Fixed effects: **–0.308** (CI, –0.629 to 0.014) (favors 2x/wk) Random effects: **–0.299** (–0.759 to 1.199)

SES, standardized effect size

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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)

Quantity/Quality, Studies	Quality, Body of Evidence	Direction of Findings	Magnitude of Benefit
Unipolar vs bipolar MDD Dierckx et al., 2012 (fair SR/MA; 6 cohort studies of unknown quality) 1106 pts	**Insufficient** Inconsistency across studies Heterogeneity in pooled estimate Unknown applicability to the population of interest	No difference	**OR of remission, 1.08** (95% CI, 0.75 to 1.57).
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	**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)	*Less* effective in confirmed TRD	**OR of remission, 0.52** (95% CI, 0.39 to 0.69)

ECT: KQ #3 (con't)

Quantity/Quality, Studies	Quality, Body of Evidence	Direction of Findings	Magnitude of Benefit
Subgroups: Psychosis retardation, agitation Post hoc analysis of 2 related RCTs	**Low** Small quantity data Lack of corroboration by analyses of other trials	Differential effectiveness of ECT according to electrode placement and dose – same in subgroups as overall.	
Age, race/ethnicity, gender, disease severity, disease duration, symptom type, or comorbidities	**Insufficient** No data	---	---

ECT: KQ #4

- See Findings for rTMS, KQ #4

ECT: Recap

Outcome *(# Studies)*	Direction of Findings *(Quality of Evidence)*
KQ #1a:* Depression relief, vs sham (2 RCTs) or psychotx (1 RCT) *3 fair RCTs (134 pts)*	*(low)* Unknown relevance of posttx difference.
KQ #1b: Bifrontal (vs unilateral or bilateral [bitemporal]) *1 SR/MA (8 RCTs)*	*(low)*
KQ #1b: Bilateral (vs unilateral) *1 SR/MA (22 RCTs)*	*(moderate)*
KQ #1b: High dose (vs low dose) *1 SR/MA (6 RCTs)*	*(moderate)*
KQ #1b: 3x/wk (vs once/wk) *1 SR/MA (6 RCTs)*	*(low)*

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

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ECT: Recap (con't)

Outcome *(# Studies)*	Direction of Findings *(Quality of Evidence)*
KQ #2: Safety, vs sham	*(low)* Generally safe; cognitive decline possible, usually transient
KQ #3: Subgroups (psychosis, retardation, agitation): Differential effectiveness of ECT according to electrode placement and dose *Post hoc analysis of 2 RCTs*	*(low)* *
KQ #4: See Findings for rTMS	

*Uncertain generalizability to current typical tx parameters.

Findings: rTMS

rTMS: KQ #1a

Quantity/Quality, Studies	Quality, Body of Evidence	Direction of Findings	Magnitude of Benefit
Depression relief, rTMS vs sham AHRQ/Gaynes et al., 2011 (good SR/MA; 24 fair to good RCTs) 3 additional RCTs (fair) 1372 pts total	**Moderate** Slight inconsistency	Favored rTMS	***WMD in change scores, depressive severity:*** **5.92** (CI, -8.15 to -3.70) (I^2=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.) Study results favored rTMS but differences were not consistently significant
Durability of benefit, rTMS vs sham 7 RCTs (fair to good)	**Low** Inconsistency Heterogen-eity in measure-ment 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)

Quantity/Quality, Studies	Quality, Body of Evidence	Direction of Findings	Magnitude of Benefit
Depression relief, rTMS vs ECT 5 RCTs (4 fair, 1 poor) 261 pts	**Low** Study weaknesses Small volume of data Inconsistency	Comparable or possible superiority of rTMS (2 RCTs) Favored ECT (3 RCTs)	***In the 3 RCTs favoring ECT (significant differences):*** Posttx HAM-D difference: CI, 3.40 to 14.05 (no point estimate) Difference in HAM-D change from BL: 36% points Risk difference, response: 37% points Risk difference, partial remission: 26% points Risk difference, remission: 42% points
Depression relief, rTMS+ECT vs ECT 2 RCTs (fair) 44 pts	**Low** Study weaknesses Sparse data	Comparable	-----
Vs tx as usual, psychotx, tDCS, DBS	Insufficient No data	---	---

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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)

Quantity/Quality, Studies	Quality, Body of Evidence	Direction of Findings	Magnitude of Benefit
QOL/ function 5 RCTs (at least fair) 275 pts	**Low** Small quantity of data Inconsistency	Conflicting findings, rTMS vs sham Comparable, rTMS vs ECT or rTMS+ECT vs ECT	Improvements, where observed, were very small, i.e., negligible to 2.2 points on 100-point scales
rTMS as maintenance tx	**Insufficient** No data	---	---

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

Source	Change in Score Within Tx Arms	Response* Within Tx Arms	Remission* Within Tx Arms
STAR*D, Step 2 (1 AD failure) (Rush et al., 2006) 1475 pts	---	---	30.6%
STAR*D, Step 3 (2 AD failures) 622 pts; 2006	---	---	14.3%
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.)	Switch: 39.8% Augmentation:38.1% Maintenance: 27.3% (CI overlap.)	Switch: 22.3% Augmentation: 27.2% Maintenance: 16.8% (CI overlap.)
rTMS arms of 25 selected RCTs Published 1990s to 2013		15% to 63.2%	12% to 57%
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.

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rTMS: KQ #1b

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

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rTMS: KQ #2

- 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

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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

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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

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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.

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rTMS: Recap

Outcome *(# Studies)*	Direction of Findings *(Quality of Evidence)*
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)*	*(low)* ? Conflicting findings, rTMS vs sham Comparable, rTMS vs ECT or rTMS+ECT vs ECT

*__Insufficient evidence for__ rTMS vs usual tx, psychotx, tDCS, or DBS.

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rTMS: Recap (con't)

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

rTMS: Recap, KQ #4

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

Findings: tDCS

tDCS: KQ #1a

Quantity/ Quality, Studies	Quality, Body of Evidence	Direction of Findings	Magnitude of Benefit
Depression relief, vs sham 2 MAs (1 good [Berlim et al., 2013c], 1 fair [Kalu et al., 2012]), including 7 RCTs) 1 additional RCT (good) 320 pts total	**Low** Small quantity of data Inconsis-tency Im-precision	Favored tDCS (NS, pooled response and remission)	***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) ***Pooled response (rTMS, 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) . **NNT 10*** ***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*** ***Difference, mean MADRS (tDCS vs sham):*** **-5.6** (CI, -1.30 to -10.01; *P*=0.01) (1 RCT) ***Difference, mean MADRS (tDCS+sertraline vs sham+sertraline):*** **-8.5** (CI, -2.96 to -14.03; *P*<0.001) (1 RCT) ***Remission (OR, tDCS vs sham):*** **4.3** (CI, 1.2 to 15.6; *P*=0.02) (1 RCT) ***Remission (OR, tDCS vs sham :* 8.6** (CI, 2.5 to 29.1; *P*<0.001) (1 RCT)

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

tDCS: KQ #1a (con't)

Quantity/ Quality, Studies	Quality, Body of Evidence	Direction of Findings	Magnitude of Benefit
Durability of benefit 2 RCTs (not rated), 2 case series (very poor)	**Insufficient** Very small quantity of controlled data Posttx effect NS in 1RCT	Sustained or additional benefit up to 1 mo	Positive results maintained at 1 mo (1 RCT, 2 case series) Difference increased in favor of tDCS (1 RCT)
Maintenance tx w/ continuing tDCS 2 RCTs (1 good, 1 not rated) 30+ pts	**Insufficient** Very small quantity of data	Sustained or additional benefit	Response persisted mean 11.7 wks (1 RCT); reduction in symptom scores increased (1 RCT)
QOL/function	**Insufficient** No data	---	---

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

Source	Change in Score Within Tx Arms	Response* Within Tx Arms	Remission* Within Tx Arms
STAR*D, Step 2 (1 AD failure) (Rush et al., 2006) 1475 pts	---	---	30.6%
STAR*D, Step 3 (2 AD failures) 622 pts; 2006	---	---	14.3%
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.)	Switch: 39.8% Augmentation:38.1% Maintenance: 27.3% (CI overlap.)	Switch: 22.3% Augmentation: 27.2% Maintenance: 16.8% (CI overlap.)
Berlim et al., 2013c tDCS arms of 6 RCTs, 201 pts; 2006–2012		23.2%	12.2%
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.

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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

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tDCS: KQ #2

- 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).

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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)

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tDCS: Recap

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

**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

DBS: KQ #1a

Quantity/Quality, Studies	Quality, Body of Evidence	Direction of Findings	Magnitude of Benefit
Depression relief, vs sham 5 prospective uncontrolled studies, including 1 w/ sham lead-in phase (4 poor, 1 very poor) 86 pts	**Insufficient** Small quantity of data Poor/very poor studies	Improvement w/ respect to BL*	***Response rate:*** 40%–60% at 6 mos (4 studies); 29%–55% at 12 mos (3 studies). ***Remission rate:*** 18%–35% at 6 mos (3 studies); 18%–36% at 12 mos (2 studies)
Durability of benefit 5 studies (as above)	**Insufficient** Small quantity of data Poor/very poor studies Inconsistency	Variable	Improvement vs decline after 6 mos was inconsistent across studies.
QOL/function 2 prospective uncontrolled studies (2 poor) 34 pts	**Insufficient** for very small quantity of data and poor/very poor studies	Improvement w/ respect to BL*	***Increase in GAF score:*** 18.4 points at 2 yrs (P=0.0009); 28.3 points at 1 yr (P<0.001) (1–100 scale)

*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

DBS: KQ #2

- 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 #3

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

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DBS: Recap

- Evidence for all KQs was insufficient (very low quality or nonexistent)

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Practice Guidelines and Payer Policies

Practice guidelines

Sponsor	Relevant Recommendations	Quality *
APA – MDD (2010)	**No definition of TRD.** "Numerous" **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 psychotx have been ineffective and may be offered during the continuation phase. **rTMS may be considered**; less evidence than for ECT.	5 (fair)
APA – Bipolar (2002; 2005)	**No definition of TRD**. **ECT** may be considered for severe or **tx-resistant** bipolar depression.	5 (fair)
CANMAT – MDD (Kennedy et al., 2009)	**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.**	5 (fair)
CANMAT – Bipolar (Yatham et al., 2013)	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**.	3 (poor)

*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)

Sponsor	Relevant Recommendations	Quality *
ICSI (2012)	ADs and/or referral for psychotx for MDD. **TRD defined as failure to achieve remission** (HAM-D_{17} <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)

Sponsor	Relevant Recommendations	Quality *
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-D_{17} ≤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

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Practice guidelines: recap

Guideline Sponsor	ECT	rTMS	tDCS	DBS
APA	Recommended for TRD (unipolar and bipolar)	May be considered for TRD	No recommendation	No recommendation
CANMAT	Recommended for TRD (unipolar and bipolar)	Recommended for TRD (unipolar) No recommendation for bipolar	No recommendation	Investigational
ICSI	Recommended for TRD	No recommendation	No recommendation	No recommendation
NICE	Recommended for TRD	For research only	No recommendation	No recommendation
VA/DoD	Recommended for TRD	No recommendation	No recommendation	No recommendation

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Selected payer policies

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

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

KQ	ECT	rTMS	tDCS	DBS
#1a: Effective vs sham?*	Depression: Yes (low) Durability: I QOL/fxn: I	**Depression: Yes (moderate)** Durability: A few weeks (low) QOL/fxn: Yes (low)	Depression: Yes (low) Durability: I QOL/fxn: I	I
vs other nonpharm tx?	See rTMS	rTMS vs ECT: Mixed results rTMS+ECT = ECT (low) QOL/fxn: Negligible to small effect (low)	I	
vs usual care or pharmacotx?	I	I	I	I
#1b: Effect varies by tx parameter?	Bifrontal = Uni/bitemp (low) **Bilateral > Uni (moderate)** **High dose > Low dose (moderate)** 3x/wk > 1x/wk (low)	I	I	I
#2: Safe?	Overall, yes (low)	**Overall, yes (moderate)**	Safe (low)	I (potentially serious AEs)
#3: Effect varies by pt factor?	Confirmed TRD < Unclear med history (low) No association w/ psychosis, retardation, agitation (low)	Duration of episode, gender, uni- vs bipolar, degree of medication resistance: No assn (low).	Baseline severity: No association (low)	I
#4	rTMS vs AD: May be cost saving (1 study) ECT vs rTMS: *Not* cost-effective, rTMS-then-ECT for nonresponder: Dominates ECT alone (1 study) rTMS vs ECT: *Not* cost-effective (1 study)		I	I

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

** Clinical relevance uncertain*

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

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Ren J, Li H, Palaniyappan L, et al. Repetitive Transcranial magnetic stimulation versus electroconvulsive therapy for major depression: A systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014. PMID 24556538.

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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

HTCC Coverage and Reimbursement Determination Analytic Tool

HTA's goal is to achieve *better health care outcomes* for enrollees and beneficiaries of state programs by paying for proven health *technologies that work*.

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[1] as expressed by the following standards[2]:

- 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[3]:

- 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).

[2] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

[3] The principles and standards are based on USPSTF Principles at: http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm

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[4] 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.

Not Confident	Confident
Appreciable uncertainty exists. Further information is needed or further information is likely to change confidence.	Very certain of evidentiary support. Further information is unlikely to change confidence

[4] Based on GRADE recommendation: 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

Sponsor, Title	Relevant Recommendations	Quality*/ Comments
APA (2010) (MDD)	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.	5 (no critical appraisal of evidence and unclear link between quality/quantity of evidence and recommendations)
APA (2002); APA (2005) (BD)	No definition of TRD. ECT may be considered for severe or tx-resistant bipolar depression.	5 (no critical appraisal of evidence and unclear link between quality/quantity of evidence and recommendations)
CANMAT (2009) (MDD)	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.	5 (intended pt population for rTMS and whether it may be considered in the absence of failed ECT were unclear)
CANMAT (2013) (BD)	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.	3 (no linking of recommendations w/ evidence)
ICSI (2012)	No definition of TRD. ADs and/or referral for psychotherapy for MDD. TRD defined as failure to achieve remission (HAM-D_{17} <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 (criteria for selecting evidence was not reported; body of evidence limitations NR; methods for formulating recommendations was NR)

Sponsor, Title	Relevant Recommendations	Quality*/ Comments
NICE (2009)	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.	7
VA/DoD (2009)	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 <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.	6 (literature search only through December 2006; procedure for updating guideline NR)

*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?

Safety Outcomes	Safety Evidence
Cognitive decline/effects	
Seizure	
Local effects (e.g., pain, itching)	
Treatment emergent mania	
Efficacy – Effectiveness Outcomes	**Efficacy / Effectiveness Evidence**
Depression relief	
Relapse rates	
Remission	
Durability of benefit	
Quality of Life/Function	
Special Population / Considerations Outcomes	**Special Population Evidence**
Unipolar vs bipolar MDD	
TRD confirmed vs lack of well documented failure	
Psychosis/retardation/agitation	
Age	

Race	
Gender	
Disease severity	
Disease duration	
Symptom type	
Comorbidities	
History of prior treatment	
Cost	**Cost Evidence**
Cost effectiveness	
ICER	

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:

	Unproven (no)	**Equivalent** (yes)	**Less** (yes)	**More** (yes)
Effective				
Safe				
Cost-effective				

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?