Washington State Health Care Authority

Vagal nerve stimulation for epilepsy and depression

Clinical Expert

Edward J. Novotny, MD

Director, Epilepsy
Alvord, Gerlich and Rhodes Family Endowed Chair in Pediatric Epilepsy,
University of Washington School of Medicine

Director Epilepsy Program, Seattle Children's Hospital

Professor of Neurology and Pediatrics,
Adjunct Professor of Radiology and Neurosurgery,
University of Washington School of Medicine

Applicant Name: Edward J. Novotny, Jr., MD

Address: Seattle Children's Hospital and Research Institute
Neurology, M/S MB.7.420, 4800 Sandpoint Way NE
Seattle, WA 98105

1. Business Activities

(a) If you or a member of your household was ***an officer or director of a business*** during the immediately preceding calendar year and the current year to date, provide the following:

Title	Business Name & Address	Business Type
N/A		

(b) If you or a member of your household ***did business under an assumed business name*** during the immediately preceding calendar year or the current year to date, provide the following information:

Business Name	Business Address	Business Type
N/A		

2. Honorarium

If you ***received an honorarium of more than $100*** during the immediately preceding calendar year and the current year to date, list all such honoraria:

Received From	Organization Address	Service Performed
Zogenix , EMERYVILLE, CA.	Scientific Advisory Board	

3. Sources of Income

(a) Identify ***income source(s) that contributed 10% or more of the combined total gross household income*** received by you or a member of your household during the immediately preceding calendar year and the current year to date.

Source Name & Address	Received By	Source Type
Childrens University Medical Group	E. J. Novotny, MD	Salary
4500 Sand Point Way NE, Suite 100, Seattle, WA 98105		
University of Washington Physicians	Fuki Hisama, MD	Salary
1959 NE Pacific St, Seattle, WA 98195		
University of Washington		Salary

(b) Does any income source listed above relate to, or could it reasonably be expected to relate to, business that has, or may, come before the Committee?

☒ Yes ☐ No

If "yes", describe: Click here to enter text.

As a pediatric epileptologist and director of the Epilepsy Program at Seattle Children's Hospital, I am engaged in the clinical care and use of health technology related to epilepsy and neurological disorders.

(c) Does an income source listed above have a legislative or administrative interest in the business of the Committee?

☐ Yes ☒ No

If "yes", describe: Click here to enter text.

4. Business Shared With a Lobbyist

If you or a member of your household ***shared a partnership, joint venture, or similar substantial economic relationship with a paid lobbyist***, were employed by, or employed, a paid lobbyist during please list the following:

(Owning stock in a publicly traded company in which the lobbyist also owns stock is not a relationship which requires disclosure.)

Lobbyist Name	Business Name	Type Business Shared
N/A		

Provide the information requested in items 5, 6, and 7 below only if:
(a) Your response involves an individual or business if you or a member of your household did business with, or reasonably could be expected to relate to business that has or may come before the Health Technology Clinical Committee.
(b) The information requested involves an individual or business with a legislative or administrative interest in the Committee.

5. Income of More Than $1,000

List each source (***not amounts***) of income over $1,000, other than a source listed under question 3 above, which you or a member of your household received during the immediately preceding calendar year and the current year to date:

Income Source	Address	Description of Income Source
Zogenix , EMERYVILLE, CA.		Scientific Advisory Board - Travel expenses

6. Business Investments of More Than $1,000

(Do not list the amount of the investment or include individual items held in a mutual fund or blind trust, a time or demand deposit in a financial institution, shares in a credit union, or the cash surrender value of life insurance.)

If you or a member of your household had a personal, beneficial interest or investment in a business during the immediate preceding calendar year of more than $1,000, list the following:

Business Name	Business Address	Description of Business
N/A		

7. Service Fee of More Than $1,000

(Do not list fees if you are prohibited from doing so by law or professional ethics.)

List each ***person for whom you performed a service for a fee of more than $1,000*** in the immediate preceding calendar year or the current year to date.

Name	Description of Service
N/A	

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

Print Name: Edward J. Novotny, Jr., MD

Check One: ☒ Committee Member ☐ Subgroup Member ☐ Contractor

[redacted] 4/10/2020

Signature Date

CURRICULUM VITAE

Edward John Novotny, Jr., M.D.

Birth Date: November 18, 1953 Birth Place: White Plains, New York

Office address: Seattle Children's Hospital
4800 Sandpoint Way NE
Neurology, Box 359300 M/S – MB.7.420
Seattle, WA 98105
Email - ejn4@uw.edu

Marital Status: Married Children: None

Citizenship: U.S.A.

EDUCATION:

Undergraduate Education:

B.S. University of California, Irvine
Irvine, CA 92717
Dates: 9/71 to 6/75
Majors: Biology (B.S.), Chemistry (B.S.) Cum Laude

Medical Education:

M.D. Saint Louis University Medical School
1402 S. Grand Ave.
Saint Louis, MO 63104
Dates: 8/75 to 5/79

POSTGRADUATE TRAINING:

Internship: 7/79 to 6/80 University of California, Davis Medical Ctr.
2315 Stockton Blvd.
Sacramento, CA 95817

Residencies:

1. 7/80 to 6/81 Pediatrics (PL1 and PL2)
University of California, Davis Medical Ctr.
2315 Stockton Blvd.

Sacramento, CA 95817

2. 7/81 to 6/84 — Neurology (Pediatric)
Stanford University Medical Center
Department of Neurology, Rm C338
Stanford, CA 94305

Fellowships:

1. 7/84 to 6/86 — Neurology (EEG/Epilepsy)
Stanford University Medical Center
Department of Neurology, Rm C338
Stanford, CA 94305

2. 7/87 to 6/89 — Neurology (NMR Spectroscopy)
Yale University, School of Medicine
Department of Neurology, LCI 710
333 Cedar Street
New Haven, CT 06510

ACADEMIC POSTS:

1984-1986 — Physician Specialist
Stanford University
Department of Neurology

1986-1987 — Acting Assistant Professor
Stanford University
Department of Neurology

1987-1990 — Associate Research Scientist
Yale University
Department of Neurology

1990-2000 — Assistant Professor
Yale University
Departments of Pediatrics and Neurology

1992 – 2009 — Associate Director (Pediatrics)
Yale University Clinical Neurophysiology Lab
Departments of Pediatrics and Neurology

1992 - 2009 — Director, Pediatric Epilepsy
Yale University
Departments of Pediatrics and Neurology

2000 - 2003 — Associate Professor

	Yale University Departments of Pediatrics and Neurology
2003 – 2009	Associate Professor Yale University Departments of Pediatrics, Neurology and Neurosurgery
2003 to 2006	Director, Clinical Neurophysiology Yale University Training Program, Departments of Pediatrics and Neurology
2009 – Present	Professor University of Washington Departments of Neurology and Pediatrics
2010 – Present	Professor (adjunct) University of Washington Departments of Radiology and Neurosurgery

HOSPITAL APPOINTMENTS:

1984-1987	Attending, Neurology Stanford University Medical Center
1987-2009	Attending, Neurology Yale-New Haven Hospital
1990-2009	Attending, Pediatrics Yale-New Haven Hospital
2009 – present	Attending, Pediatrics and Neurology Seattle Children's Hospital Director, Epilepsy Program
2009 – Present	Attending, Neurology University of Washington Medical Center

PROFESSIONAL AWARDS:

1. Awarded the William Gowers Fellowship in Clinical Epilepsy Research from the Epilepsy Foundation of America for the year 7/1/84 to 6/30/85.

2. Awarded the S. Weir Mitchell Award by the American Academy of Neurology in 1985.
3. Fellow in the Epilepsy Training Program sponsored by the National Institutes of Health awarded to the Department of Neurology at Stanford University, 5-T32-NS07280-01. (7/1/85 to 6/30/86).
4. National Research Service Award from National Institutes of Health for research in the area of biochemistry, "In vivo NMR spectroscopic investigations in epilepsy", at Yale University Department of Neurology. 1 F32 NS08252-01. (8/1/87 to 7/30/89)
5. FIRST Award NIH (NINDS), " In vivo $^{1}H/^{13}C$ NMR Studies of Neonatal seizures" (1R29 NS28790-01). 9/1/90 to 8/31/95.
6. *Best Doctors in America* – Northeast region – 1996, 1998, 1999, 2000; Best Doctor in New York Magazine – 2007, 2008, 2009, ; US News Health 2011-2012; Top Doctors Seattle 2011-2019
7. Teaching Attending of the year Department of Neurology Residents – 1997-1998
8. Member American Heart Association Brain 1 Peer Review Committee National Research Program – 4/2002, 4/2003, 10/2003, 4/2004
9. Ad-Hoc reviewer NIH Study section(s): Neurological Sciences and Disorders A 10/1998; Clinical Research Review Committee 6/1999; Biophysical Chemistry Study Section 10/2002; Developmental Brain Disorders Study Section 6/2003 – 11/2004; Special Emphasis Panel – NIDA 6/2007; NIDA - 6/2009
10. Elected Fellow of American Clinical Neurophysiology Society (1992) – FACNS
11. Elected Fellow of American Academy of Neurology (2014) – FAAN
12. Elected Fellow of American Epilepsy Society (2016)- FAES

PROFESSIONAL ORGANIZATIONS/COMMITEES:

American Academy of Neurology (1982)
S. Weir Mitchell Award (1985); Computers and Neurology Workshop Instructor (1995 – 1997); Epilepsy Section Member (2000 -); Child Neurology Section Member (2000 -). Dreyfuss-Penry Award Committee (2009 – present); Fellow (2014 to present)

American Epilepsy Society (1984) - Scientific Program Committee (1995-97), Investigator's Workshop Committee (1998-2000), Technology Committee (2001); Pediatric Content Committee (2006-present); Web Committee (2008 –2010); Chair, Pediatric Content Committee (2011-2013); Council on Education (2011-13); Clinical Investigators Workshop Committee (2011-present); Chair, Clinical Investigators Workshop Committee (2014-present); Fellow (2016 – present)

American Clinical Neurophysiology Society (1986) - Scientific Program Committee 1996-1997; Fellow (1992).

Child Neurology Society (1984) - Junior membership committee 1986-1987;
Research Committee 1990 - 1993; Scientific Program Committee 1995-1999; 2000-2006, Electronic Communications Committee 1997- 2004. 2006 – 2009.

International Society for Magnetic Resonance in Medicine (1987)

International Child Neurology Association (1988)

Society for Pediatric Research (1993) – Scientific Program Committee (Neurology) 2001 - 2004

Society for Neuroscience (1995)
Pediatric Neurology – Editorial board member – 2000 - 2006
Clinical Research Review Committee – Yale University Children's Clinical Research Center – 1996 – 2004
Information Technology Committee – Yale University School of Medicine – 2000 - 2005
General Advisory Committee – Yale University General Clinical Research Center – 2003 – 2006
Pediatric Protocol Committee – Yale University Clinical Research Center – 2000 - 2009

BOARD CERTIFICATION:

American Board of Pediatrics (1/19/1986, #33114)
American Board of Psychiatry and Neurology (Neurology with special qualification in Child Neurology) (2/1986, #567)
American Board of Clinical Neurophysiology (1989)
American Board of Psychiatry and Neurology (Neurology with special qualification in Clinical Neurophysiology) (4/1994, #402; recertified 8/2004)
American Board of Psychiatry and Neurology (subspecialty Epilepsy) (8/11/2014, #638)

LICENSES:

Physician and Surgeon's License (California G, 7/80; Connecticut #28557, 9/87; Washington - MD 60078540, 7/2009 exp 11/18/2021; Montana #68076 7/2018 exp. 3/31/2020)

RESEARCH EXPERIENCE:

Past:

William Gower's Fellowship – Epilepsy Foundation of America -"Investigation of Neonatal seizures post hypoxic-ischemia" – 7/1/84 – 6/30/85

Fellow, Epilepsy Training Program Stanford University – T32-NS07280-01 (David Prince) 7/1/85 – 6/30/86

Fellow, NMR Spectroscopy – NRSA 1 F32 NS08252-01 "In vivo NMR spectroscopic investigations in epilepsy". Yale University 7/1/87 –6/30/89

Principal Investigator - FIRST Award NIH (NINDS), "In vivo $^{1}H/^{13}C$ NMR Studies of Neonatal seizures" (1R29 NS28790-01). 9/1/90 to 8/31/95

Principal Investigator - Juvenile Diabetes Foundation - "Brain Glucose Transport in Nondiabetic and Insulin Dependent Diabetic Subjects Investigated by In Vivo NMR Spectroscopy", 9/1/91 – 8/31/92.

Principal Investigator - P20NS32578-01 (Ment) "Basic mechanisms of cortical injury--relevance

to IVH". Project 2 - NMR investigations of Hypoxic ischemic Injury. 9/30/93 – 8/31/96.

Principal Investigator – Epilepsy Foundation of America – "Multinuclear NMR studies of the Ketogenic Diet in Children." 7/1/96 – 6/30/97.

Collaborator - 1R01NS31146-01 (Berg, A) "Risk and predictors of intractable epilepsy in children" – 1/15/93 –1/14/97.

Principal Investigator - M01RR06022-060781 Children's Clinical Research Center Grant - "Intensive neurodiagnostic monitoring in Pediatric Epilepsy". 12/1/89 – 11/30/2004.

Investigator - 1 PO1-HD 32573-01 (Haddad) NIH/NCHHD "Hypoxia in Development: Injury and Adaptation Mechanisms" Project 4: Brain Metabolism and Function in Hypoxia. 2/1/95 - 1/31/2004

Investigator - RO1 NS 35918 (Haddad) NIH/NINDS
"Ionic and Metabolic Mechanisms in Hypoxic Neuronal Injury". 2/1/97-1/31/2002

Principal Investigator - RO1-NS 38175 NIH/NINDS
"Cerebral GABA in Cryptogenic Generalized Epilepsy". 1/4/99-11/30/2003

Principal Investigator - R21 DA015908 9/27/2002 – 6/30/2005
"NMR Studies of Brain Glutamate Turnover in Development"

Investigator - JDRF - (Rothman, P.I., Project 3) Juvenile Diabetes Research Foundation
6/01/00-5/31/04 "CNS Effects and Prevention of Hypoglycemia in Human Type 1 Diabetes"

Consultant - R01 HL070919 9/3/2002 – 7/31/2006
"Sleep Mechanisms in Children: Role of Metabolism"

Investigator – R01NS 044102 2/1/2003 – 1/31/2008
"Anticipating seizures in epileptic networks"

Principal Investigator (Yale) - UO1 NS045911 10/2003 – 11/2008
"Childhood Absence Epilepsy: Rx, PK-PD Pharmacogenetics"

Investigator- R01NS047605 7/1/2005 – 6/30/2009
"Epileptogenic Tissue Localization using EEG-fMRI"

Investigator - R01NS055829 (Blumenfeld) 8/2/2006 – 1/31/2010
"Functional Neuroimaging in Childhood Absence Epilepsy"

Investigator - 5U01NS053998-03 (Lowenstein) 5/1/2010 – 4/30/2013
"THE EPILEPSY PHENOME/ GENOME PROJECT (EPGP)"

Collaborator/Investigator – (Grabowski) - RC4 NS073008 30-SEP-2010 – 31-AUG-2013
IBIC: Integrated Brain Imaging Center for the University of Washington

Mentor – (Weaver) - K01 MH086118 10-AUG-2010 - 31-JUL-2015
Defining the Dynamics of the Default Network with Direct Brain Recordings and functional MRI

Key Personnel – (Oakley) - K08 NS071193 15-APR-2011 - 31-MAR-2016
Brain regions contributing to seizures as a function of age and body temperature in a mouse model of severe myoclonic epilepsy in infancy

Consultant – (Chaovalitwongse) - NSF
Graph-Theoretic Analysis of Functional Connectivity MRI as a Non-Invasive Test for Lateralization and Localization of the Epileptic Focus in Temporal Lobe Epilepsy

Pediatric Epilepsy Research Foundation (A. Berg PI; Site PI) **9/1/2013 – 7/31/2017**
Early Onset Epilepsy Consortium
The Early Onset Epilepsy Consortium (EOEC) study is a follow up of a retrospective study that was performed at Seattle Children's in 2012. In the current proposal, we will identify all children seen at Seattle Children's Hospital between the ages of 1 month and 3 years over a 2 year period.

Fycompa (E. Novotny) **2/6/2017-5/31/2019**
A Retrospective Multicenter Study to Investigate Dosage, Efficacy, and Safety of Fycompa® in Routine Clinical Care of Patients With Epilepsy

Current:
Pediatric Status Epilepticus Research Group (pSERG); (T. Loddenkemper PI; Site Co-PI) **7/2017 – present (L. Morgan/E. Novotny).** The Pediatric Status Epilepticus Research Group (pSERG) is a national consortium focusing on outcomes of status epilepticus.

Critical Care EEG Monitoring Consortium. A forum for collaborative research in Critical Care EEG Monitoring and promote quality improvements and standardization of the clinical practice of Critical Care EEG Monitoring. **7/2017 – present (L. Bozarth/E. Novotny).** Upload CCEEG data to CCEMRC data repository.

Pilot data on comparative effectiveness outcomes from Hypothalmic Hamartoma surgical intervention. **4/24/2018 – present (J. Ojemann).**

Psychosocial impacts on the Ketogenic Diet **7/2/2018 – present (R. Fraser)** The impacts of psychosocial factors on successful maintenance of the Ketogenic Diet in pediatric populations

Epileptic encephalopathy with CSWS: a review of current treatment practices. **1/6/2017 – present (J. Lopez/E. Novotny)**

E2007-G000-506 Protocol Title: A Retrospective Multicenter Study to Investigate Dosage, Efficacy, and Safety of Fycompa® in Routine Clinical Care of Patients With Epilepsy **(Novotny)**

6/2018 to 5/2019 Eisai, Inc

Eisai E2007-G000-506 clinical study. Fycompa in Clinical care of children with epilepsy
(Bozarth/Novotny) 1/2020 – present Eisai, Inc

Collaborative proposal to accelerate gene discovery in pediatric and adult epilepsy surgery **(G. Mirzaa) 1/1/2019 – 12/30/2020** Brotman Baty Institute for Precision medicine catalytic award

CDC Grant- 6 U48DP006398-01-01 "Managing Epilepsy Well 2.0 (MEW) Network - Collaborating Center" (**R. Fraser**) 9/30/2019 – 9/29/2024

PUBLICATIONS:

Journal Articles:

1. Seidenwurm D, **Novotny EJ**, Enzmann D, Marshall WM. The Neuroradiological Features of a Neurodegenerative Disorder with Mitochondrial Inheritance. AJNR 1986;7:629-632. PMID: 3088941
2. **Novotny EJ**, Singh G, Wallace DC, Dorfman LJ, Louis A, Sogg RL, Steinman L. Leber's Disease and Dystonia: A Mitochondrial Disease. Neurology 1986;36:1053-1060. PMID: 3736869
3. **Novotny EJ**, Urich H. The Coincidence of Encephalofacial Angiomatosis and Neurocutaneous Melanosis. Clin Neuropathol 1986;5:246-251. PMID: 3815935
4. **Novotny EJ**, Urich H. The Brain in Partial Trisomy 18(18q+). A case report. J Child Neurol 1987;2:1944.
5. **Novotny EJ**, Tharp BR, Coen RW, Bejar R, Enzmann D, Vaucher YE. The Significance of Positive Rolandic Sharp Waves in the Electroencephalogram of the Premature Neonate. Neurology 1987;37:1481-1486. PMID: 3306454
6. Young RSK, Cowan BE, Petroff OAC, Briggs RW, **Novotny EJ**. The effect of hypoglycemia on brain blood flow and brain energy state during neonatal seizures. Ann N Y Acad Sci 1987;508:494-496.
7. Young RSK, Cowan BE, Petroff OAC, **Novotny EJ**, Dunham SL, Briggs RW. In Vivo ^{31}P and in Vitro ^{1}H Nuclear Magnetic Resonance Study of Hypoglycemia during neonatal seizures. Ann Neurol 1987;22:622-628. PMID: 3426168
8. Petroff OAC, Young RSK, Cowan BE, **Novotny EJ**. ^{1}H Nuclear Magnetic Resonance Spectroscopy Study of Neonatal Hypoglycemia. Pediatr Neurol 1988;4:31-4. PMID: 3233106
9. **Novotny EJ**. Arthrogryposis Associated with Connatal Pelizaeus-Merzbacher Disease: Case Report. Neuropediatr 1988;19:221-223.
10. Young RSK, Chen B, Petroff OAC, Cowan BE, **Novotny EJ**, Gore JC, Wong M, Zuckerman K. The effect of diazepam on neonatal seizure: In vivo ^{31}P and ^{1}H NMR Study. Pediatr Research 1989;25:27-31. PMID: 2919113
11. Hanstock CC, Rothman DL, Shulman RG, **Novotny EJ**, Petroff OAC, Prichard JW. Measurement of Ethanol in the human brain using NMR spectroscopy. J of Studies on Alcohol 1990:51;104-107.

12. Petroff OAC, **Novotny EJ**, Ogino T, Avison M, Prichard JW. In Vivo measurements of ethanol concentration in rabbit brain by H-1 magnetic resonance spectroscopy. J of Neurochem 1990:54;1188-1195.
13. Avison MJ, Herschkowitz N, **Novotny EJ**, Petroff OAC, Rothman DL, Colombo JP, Bachmann C, Shulman RG, Prichard JW. Proton NMR Observation of phenylalanine and an aromatic metabolite in the rabbit brain in vivo. Ped Research 1990:27;566-570.
14. Young RSK, Petroff OAC, **Novotny EJ**, Wong M. Neonatal excitotoxic brain injury - Physiologic, metabolic, and pathologic findings**. Developmental Neurosci** 1990:12;210-220. PMID: 2142073
15. **Novotny EJ**. Epileptic Syndromes and Seizures in Infants. Seminars in Neurology 1990:10;366-379.
16. **Novotny EJ**. Seizures and other Abnormal Behaviors in the Newborn. Resident and Housestaff Physician 1990:36;71-74.
17. **Novotny EJ**, Ogino T, Rothman DL, Petroff OAC, Prichard JW, Shulman RG. Direct carbon versus proton heteronuclear editing of 2-^{13}C ethanol in rabbit brain in vivo: A sensitivity comparison. Magnetic Resonance in Medicine 1990:16;431-443.
18. Prichard JW, Rothman DL, **Novotny EJ**, Petroff OAC, Kuwabara T, Avison M, Howseman A, Hanstock CC, Shulman RG. Lactate Rise Detected by ^{1}H NMR in Human Visual Cortex During Physiologic Stimulation. Proc Natl Acad Sci USA 1991:88;5829-5831.
19. Gruetter R, **Novotny EJ,** Boulware SD, Rothman DL, Mason GF, Shulman GI, Shulman RG, Tamborlane WT. Direct measurement of brain glucose concentrations in humans by ^{13}C NMR spectroscopy. Proc Natl Acad Sci USA 1992:89;1109-1112.
20. Rothman DL, Hanstock CC, Petroff OAC, **Novotny EJ**, Prichard JW, Shulman RG. Localized ^{1}H NMR Spectra of Glutamate in the Human Brain. Magnetic Resonance in Medicine 1992:25;94-106.
21. Gruetter R, Rothman DL, **Novotny EJ**, Shulman RG. Localized ^{13}C NMR Spectroscopy of Myo-Inositol in the Human Brain In Vivo. Magnetic Resonance in Medicine 1992:25;204-210.
22. Gruetter R, Rothman DL, **Novotny EJ**, Shulman GI, Prichard JW, Shulman RG. Detection and Assignment of the Glucose Signal in ^{1}H NMR Difference Spectra of the Human Brain. Magnetic Resonance in Medicine 1992:27,183-188.
23. Petroff OAC, **Novotny EJ**, Avison M, Rothman DL, Alger JR, Ogino T, Shulman GI, Prichard JW. Cerebral lactate turnover after electroshock: in vivo measurements by 1H/13C magnetic resonance spectroscopy. J Cereb Blood Flow Metab 1992:12 (6);1022-1029. PMID: 1400641
24. Rothman DL, **Novotny EJ**, Shulman GI, Howseman AM, Petroff OAC, Mason G, Nixon T, Hanstock CC, Prichard JW, Shulman RG. ^{1}H -[^{13}C] NMR Measurements of [4-^{13}C]-Glutamate Turnover in Human Brain. Proc Natl Acad Sci USA 1992:89;9603-9606.
25. Rosen CL, **Novotny EJ**, D'Andrea LA, Petty EM. Klippel-Feil Sequence and Sleep Disordered Breathing in Two Children. Amer Rev Resp Dis 1993: 147;202-204.
26. Spencer SS, Katz A, Ebersole JE, **Novotny E**, Mattson R. Ictal EEG changes with corpus callosum section. Epilepsia 1993:34;568-573. PMID: 8504788
27. Chen W, **Novotny EJ**, Zhu X-H, Rothman DL, Shulman RG. Localised ^{1}H NMR

Measurement of Glucose Consumption in the Human Brain During Visual Stimulation. Proc Natl Acad Sci USA 1993:90;9896-9900.

28. **Novotny EJ**. Neonatal Seizures. Seminars in Perinatology 1993:17;315-356.
29. Gruetter R, **Novotny EJ**, Boulware SD, Rothman DL, Mason GF, Shulman GI, Tamborlane WV, Shulman RG. Non-invasive measurements of the cerebral steady-state glucose concentration and transport in humans by 13C nuclear magnetic resonance. Adv in Exp Med & Biol. 1993:331:35-40.
30. Shaywitz BA, Anderson GM, **Novotny EJ**, Ebersole JS, Sullivan CM, Gillespie SM. Aspartame Has No Effect on Seizures or Epileptiform Discharges in Epileptic Children. Ann Neurol 1994:35;98-103.
31. Gruetter R, **Novotny EJ**, Boulware SD, Mason GF, Rothman DL, Prichard JW, Shulman RG. Localised ^{13}C NMR Spectroscopy in the Human Brain of Amino acid labeling from [1-^{13}C] Glucose. J Neurochem 1994:63;1377-1385.
32. **Novotny EJ**, Avison M, Herschkowitz N, Petroff OAC, Prichard JW, Seashore MR, Rothman DL. In Vivo Measurement of Phenylalanine in Human Brain by Proton Nuclear Magnetic Resonance Spectroscopy. Pediatr Res 1995:37;244-249.
33. Mason G, Gruetter R, Rothman DL, Behar KL, Shulman RG, **Novotny EJ**. Simultaneous Determination of the rates of the TCA cycle, glucose utilization, and alpha-ketoglutarate/glutamate exchange and glutamine synthesis in human brain by NMR. J Cereb Blood Flow Metab 1995:15;12-25. PMID: 7798329
34. **Novotny EJ**. Overview - The Role of NMR Spectroscopy in Epilepsy. Magnetic Resonance Imaging 1995:13;1171-1173.
35. Berg AT, Levy SR, **Novotny EJ**, Shinnar S. Predictors of Intractable Epilepsy in Childhood: A Case-Control Study. Epilepsia 1996:37;24-30.
36. Gruetter R, **Novotny EJ**, Boulware SD, Rothman DL, Shulman RG. ^{1}H NMR Studies of Glucose Transport in the Human Brain. J Cereb Blood Flow Metab 1996:16;427-
37. Kang P**, Novotny EJ.** A two year old girl with acute onset of seizures and progressive encephalopathy. Curr Opin Pediatr. 1997, 9:558-564.
38. **Novotny EJ**. The Role of Clinical Neurophysiology in the Management of Epilepsy. J of Clin Neurophysiology 1998 15:96-108.
39. Shen JS, **Novotny EJ**, Rothman DL. In vivo lactate and β-hydroxybutyrate editing using a pure phase refocusing pulse train. Magnetic Resonance in Medicine 1998 40:783-788.
40. **Novotny E**, S. Ashwal, M. Shevell. Proton NMR Spectroscopy: An Emerging Technology in Pediatric Neurology Research. Pediatr Res 1998, 44:1-10.
41. Levy SR**,** Berg AT**,** Testa F, **Novotny EJ**, Chiappa K. Comparison of digital and conventional EEG interpretation. J. Clin Neurophysiology 1998 15:476-80
42. **Novotny EJ,** Hwang J-H, Rothman DL, Matalon R. Cerebral Amino acids and Metabolites in Amino Acylase II deficiency: Alterations with Dietary Therapy. Molecular and Chemical Neuropathology 1999
43. **Novotny EJ**, Hyder F, Shevell M, Rothman D. GABA changes with vigabatrin in the developing human brain Epilepsia 1999 40:462-466. PMID: 10219272
44. Shevell MI, Ashwal S**, Novotny E.** Proton magnetic resonance spectroscopy: clinical applications in children with nervous system diseases. Semin Pediatr Neurol 1999 6:68-77.
45. Masuoka LK, Anderson AW, Gore JC, McCarthy G, Spencer DD, **Novotny EJ**

Functional magnetic resonance imaging identifies abnormal visual cortical function in patients with occipital lobe epilepsy. Epilepsia 1999 Sep; 40(9):1248-53

46. Boles RG, Seashore MR, Mitchell WG, Kollros PR, Mofidi S, **Novotny EJ.** Glucose transporter type 1 deficiency: a study of two cases with video-EEG. Eur J Pediatr 1999 Dec; 158(12):978-83.
47. Buerstatte CR, Behar KL, **Novotny EJ**, Lai JCK. Brain regional development of the activity of -ketoglutarate dehydrogenase complex in the rat, Brain Res Dev Brain Res 2000 Dec;125:139-145.
48. **Novotny EJ**, Ariyan C, Mason GF, Haddad G, J. O'Reilly J, Behar, K.L, Differential Increase in Cerebral Cortical Glucose Oxidative Metabolism During Rat Postnatal Development is Greater In Vivo than In Vitro. Brain Res 2001 Jan;888:193-202 PMID: 11150475
49. Studholme C, **Novotny E**, Zubal IG, Duncan JS. Estimating Tissue Deformation between Functional Images Induced by Intracranial Electrode Implantation Using Anatomical MRI. Neuroimage 2001 Apr;13(4):561-76.
50. de Graaf RA, Pan JW, Telang F, Lee JH, Brown P, **Novotny EJ**, Hetherington HP, Rothman DL. Differentiation of glucose transport in human brain gray and white matter. J Cereb Blood Flow Metab. 2001 May;21(5):483-92.
51. Butchko HH, Stargel WW, Comer CP, Mayhew DA, Benninger C, Blackburn GL, de Sonneville LM, Geha RS, Hertelendy Z, Koestner A, Leon AS, Liepa GU, McMartin KE, Mendenhall CL, Munro IC, **Novotny EJ**, Renwick AG, Schiffman SS, Schomer DL, Shaywitz BA, Spiers PA, Tephly TR, Thomas JA, Trefz FK. Aspartame: review of safety. Regul Toxicol Pharmacol. 2002 Apr;35(2 Pt 2):S1-93.
52. Zaatreh MM, Spencer DD, Thompson JL, Blumenfeld H, **Novotny EJ**, Mattson RH, Spencer SS. Frontal lobe tumoral epilepsy: clinical, neurophysiologic features and predictors of surgical outcome. Epilepsia**.** 2002 Jul;43(7):727-33.
53. Cendes F, Knowlton RC, **Novotny E**, Min LL, Antel S, Sawrie S, Laxer KD, Arnold D. Magnetic resonance spectroscopy in epilepsy: Clinical issues. Epilepsia 43: 32-39 Suppl. 1 2002.
54. Motamedi M, Nguyen DK, Zaatreh M, Singh SP, Westerveld M, Thompson JL, Mattson R, Blumenfeld H, **Novotny E**, Spencer SS. Levetiracetam efficacy in refractory partial seizures, especially after failed epilepsy surgery. Epilepsia 2003 Feb;44(2):211
55. Lai JC, White BK, Buerstatte CR, Haddad GG, **Novotny EJ Jr**, Behar KL. Chronic Hypoxia in Development Selectively Alters the Activities of Key Enzymes of Glucose Oxidative Metabolism in Brain Regions. Neurochem Res 2003; 28: 933-940.
56. Pearl PL, Gibson KM, Acosta MT, Vezina LG, Theodore WH, Rogawski MA, **Novotny EJ**, Gropman A, Conry JA, Berry GT, Tuchman M. Clinical spectrum of succinic semialdehyde dehydrogenase deficiency. Neurology 2003 May 13;60(9):1413-7
57. Nguyen D, Singh S, Zaatreh M, **Novotny E**, Levy S, Testa F, Spencer SS. Hypothalamic hamartomas: seven cases and review of the literature. Epilepsy Behav. 2003 Jun;4(3):246-58.
58. Trubel HK, **Novotny E**, Lister G. Outcome of coma in children. Curr Opin Pediatr. 2003 Jun;15(3):283-7
59. **Novotny EJ Jr,** Fulbright RK, Pearl PL, Gibson KM, Rothman DL. Magnetic resonance spectroscopy of neurotransmitters in human brain. Ann Neurol. 2003;54 Suppl 6:S25-31.

60. Pearl PL, **Novotny EJ,** Acosta MT, Jakobs C, Gibson KM. Succinic semialdehyde dehydrogenase deficiency in children and adults. Ann Neurol. 2003;54 Suppl 6:S73-80.
61. Trubel H, Herman P, Kampmann C, **Novotny E**, Hyder F. Selective brain cooling from the pharynx. BIOMEDIZINISCHE TECHNIK 2003;48 (11): 298-300.
62. Blumenfeld H, McNally KA, Vanderhill SD, Paige AL, Chung R, Davis K, Norden AD, Stokking R, Studholme C, **Novotny EJ Jr**, Zubal IG, Spencer SS. Positive and negative network correlations in temporal lobe epilepsy. Cereb Cortex. 2004 Aug;14(8):892-902.
63. Trubel H, Herman P, Kampmann C, Huth R, Maciejewski PK, **Novotny E**, Hyder F. A novel approach for selective brain cooling: implications for hypercapnia and seizure activity. Intensive Care Med. 2004 Sep;30(9):1829-33. Epub 2004 Jun 08.
64. Trubel H, Herman P, Kampmann C, **Novotny E**, Hyder F. [Duration of induced seizures during selective pharyngeal brain cooling] Biomed Tech (Berl). 2004 Oct;49(10):279-81. German.
65. McNally KA, Paige AL, Varghese G, Zhang H, **Novotny EJ Jr**, Spencer SS, Zubal IG, Blumenfeld H. Localizing Value of Ictal-Interictal SPECT Analyzed by SPM (ISAS). Epilepsia. 2005 Sep;46(9):1450-64.
66. Safriel Y, Pol-Rodriguez M, **Novotny EJ**, Rothman DL, Fulbright RK. Reference values for long echo time MR spectroscopy in healthy adults. AJNR Am J Neuroradiol. 2005 Jun-Jul;26(6):1439-45.
67. Pearl PL, Capp PK, **Novotny EJ,** Gibson KM. Inherited disorders of neurotransmitters in children and adults. Clin Biochem. 2005 Dec; 38(12):1051-8. Epub 2005 Nov 18.
68. **Novotny EJ.** Metabolic Brain Imaging by Magnetic Resonance. Future Neurol 2006 1(5):659-663.
69. Shetty-Alva N, **Novotny EJ**, Shetty T, Kuo PH. Positron Emission Tomography in Rasmussen's Encephalitis. Pediatr Neurol. 2007 Feb;36(2):112-4.
70. Dion MH, **Novotny EJ Jr**, Carmant L, Cossette P, Nguyen DK. Lamotrigine Therapy of Epilepsy with Angelman's Syndrome. Epilepsia. 2007 Mar;48(3):593-6.
71. Buch K, Blumenfeld H, Spencer S, **Novotny E**, Zubal IG. Evaluating the accuracy of perfusion/metabolism (SPET/PET) ratio in seizure localization. Eur J Nucl Med Mol Imaging. 2007 Oct 16
72. Durazzo TS, Spencer SS, Duckrow RB, **Novotny EJ**, Spencer DD, Zaveri HP. Temporal distributions of seizure occurrence from various epileptogenic regions. Neurology. 2008 Apr 8;70(15):1265-71 PMID: 18391158
73. Spencer SS, Goncharova II, Duckrow RB, **Novotny EJ**, Zaveri HP. Interictal spikes on intracranial recording: behavior, physiology, and implications. Epilepsia. 2008 Nov;49(11):1881-92. PMID: 18479398
74. Strug LJ, Clarke T, Chiang T, Chien M, Baskurt Z, Li W, Dorfman R, Bali B, Wirrell E, Kugler SL, Mandelbaum DE, Wolf SM, McGoldrick P, Hardison H, **Novotny EJ**, Ju J, Greenberg DA, Russo JJ, Pal DK. Centrotemporal sharp wave EEG trait in rolandic epilepsy maps to Elongator Protein Complex 4 (ELP4). Eur J Hum Genet. 2009 Sep;17(9):1171-81 PMID: 19172991
75. Zaveri HP, Pincus SM, Goncharova II, **Novotny EJ**, Duckrow RB, Spencer DD, Spencer SS. A decrease in EEG energy accompanies anti-epileptic drug taper during intracranial monitoring. Epilepsy Res. 2009 Oct;86(2-3):153-62. PMID: 19632096
76. Goncharova II, Zaveri HP, Duckrow RB, **Novotny EJ**, Spencer SS. Spatial distribution

of intracranially recorded spikes in medial and lateral temporal epilepsies. Epilepsia. 2009 Dec 2009;50(12):2575-85. PMID: 19674048

77. Zaveri HP, Pincus SM, Goncharova II**, Novotny EJ**, Duckrow RB, Spencer DD, Blumenfeld H, Spencer SS. Background intracranial EEG spectral changes with anti-epileptic drug taper. Clin Neurophysiol. 2010 Mar;121(3):311-7. PMID: 20075002
78. **Novotny E**, Renfroe B, Yardi N, Nordli D, Ness S, Wang S, Weber T, Kurland CL, Yuen E, Eerdekens M, Venkatraman L, Nye JS, Ford L. Randomized trial of adjunctive topiramate therapy in infants with refractory partial seizures. Neurology. 2010 Mar 2;74(9):714-20.
79. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Capparelli EV, Adamson PC; Childhood Absence Epilepsy Study Group. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med. 2010 Mar 4;362(9):790-9.
80. Bai X, Vestal M, Berman R, Negishi M, Spann M, Vega C, Desalvo M, **Novotny EJ**, Constable RT, Blumenfeld H. Dynamic time course of typical childhood absence seizures: EEG, behavior, and functional magnetic resonance imaging. J Neurosci. 2010 Apr 28;30(17):5884-93. PMID: 20427649 PubMed Central PMCID: PMC2946206
81. Berman R, Negishi M, Vestal M, Spann M, Chung MH, Bai X, Purcaro M, Motelow JE, Danielson N, Dix-Cooper L, Enev M, **Novotny EJ**, Constable RT, Blumenfeld H. Simultaneous EEG, fMRI, and behavior in typical childhood absence seizures. Epilepsia 2010. Oct;51(10):2011-22. PMID: 20608963
82. Bai X, Guo J, Killory B, Vestal M, Berman R, Negishi M, Danielson N, **Novotny EJ,** Constable RT, Blumenfeld H. Resting functional connectivity between the hemispheres in childhood absence epilepsy. Neurology. 2011 Jun 7;76(23):1960-7. PMID: 21646622
83. Khanna PC, Poliakov AV, Ishak GE, Poliachik SL, Friedman SD, Saneto RP, **Novotny EJ Jr,** Ojemann JG, Shaw DW. Preserved interhemispheric functional connectivity in a case of corpus callosum agenesis. Neuroradiology. 2011 May 8. PMID: 21553342
84. Killory BD, Bai X, Negishi M, Vega C, Spann MN, Vestal M, Guo J, Berman R, Danielson N, Trejo J, Shisler D, **Novotny EJ Jr**, Constable RT, Blumenfeld H. Impaired attention and network connectivity in childhood absence epilepsy. Neuroimage. 2011 Jun 15;56(4):2209-17. PMID: 21421063 PubMed Central PMCID:
85. Negishi M, Martuzzi R, **Novotny EJ**, Spencer DD, Constable RT. Functional MRI connectivity as a predictor of the surgical outcome of epilepsy. Epilepsia. 2011Sep;52(9):1733-40. PMID: 21801165 PubMed Central PMCID: PMC3169719
86. Ishak GE, Poliakov AV, Poliachik SL, Saneto RP, **Novotny EJ Jr**, McDaniel S, Ojemann JG, Shaw DW, Friedman SD. Tract-Based Spatial Statistical Analysis of Diffusion Tensor Imaging in Pediatric Patients with Mitochondrial Disease: Widespread Reduction in Fractional Anisotropy of White Matter Tracts. AJNR Am J Neuroradiol. 2012 Apr 12
87. Wray CD, McDaniel SS, Saneto RP, **Novotny EJ Jr**, Ojemann JG. Is postresective intraoperative electrocorticography predictive of seizure outcomes in children? Neurosurg Pediatr. 2012 May;9(5):546-51.
88. Wray CD, Kraemer DL, Yang T, Poliachik SL, Ko AL, Poliakov A, Hebb AO, **Novotny EJ**, Ojemann JG. Freehand placement of depth electrodes using electromagnetic frameless stereotactic guidance. J Neurosurg Pediatr. 2011 Nov;8(5):464-7. PMID:

22044370

89. Strug LJ, Addis L, Chiang T, Baskurt Z, Li W, Clarke T, Hardison H, Kugler SL, Mandelbaum DE, **Novotny EJ**, Wolf SM, Pal DK. The genetics of reading disability in an often excluded sample: novel Loci suggested for reading disability in rolandic epilepsy. PLoS One. 2012;7(7):e40696. Epub 2012 Jul 18.

90. Wray CD, Blakely TM, Poliachik SL, Poliakov A, McDaniel SS, **Novotny EJ**, Miller KJ, Ojemann JG. Multimodality localization of the sensorimotor cortex in pediatric patients undergoing epilepsy surgery. J Neurosurg Pediatr. 2012 Jul;10(1):1-6. PMID: 22681317 PubMed Central PMCID: PMC3576481

91. Ojemann JG, Hersonskey TY, Abeshaus S, Geyer JR, Saneto RP, **Novotny EJ**, Kollros P, Leary S, Holmes MD. Epilepsy surgery after treatment of pediatric malignant brain tumors. Seizure. 2012 Oct;21(8):624-30.

92. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Adamson PC; Childhood Absence Epilepsy Study Team. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. Epilepsia. 2013 Jan;54(1):141-55. PMID: 23167925 PubMed Central PMCID: PMC3538883

93. Winawer MR, Connors R; EPGP Investigators. Evidence for a shared genetic susceptibility to migraine and epilepsy. Epilepsia. 2013 Feb;54(2):288-95.

94. Weaver KE, Chaovalitwongse WA, **Novotny EJ**, Poliakov A, Grabowski TG, Ojemann JG. Local functional connectivity as a pre-surgical tool for seizure focus identification in non-lesion, focal epilepsy. Front Neurol. 2013 May 1;4:43.

95. Poliachik SL, Poliakov AV, Jansen LA, McDaniel SS, Wray CD, Kuratani J, Saneto RP, Ojemann JG, **Novotny EJ** Jr. Tissue localization during resective epilepsy surgery. Neurosurg Focus. 2013 Jun;34(6):E8.

96. Friedman SD, Baker LD, Borson S, Jensen JE, Barsness SM, Craft S, Merriam GR, Otto RK, **Novotny EJ**, Vitiello MV. Growth hormone-releasing hormone effects on brain γ-aminobutyric acid levels in mild cognitive impairment and healthy aging. JAMA Neurol. 2013 Jul;70(7):883-90.

97. EPGP Collaborative, Abou-Khalil B, Alldredge B, Bautista J, Berkovic S, Bluvstein J, Boro A, Cascino G, Consalvo D, Cristofaro S, Crumrine P, Devinsky O, Dlugos D, Epstein M, Fahlstrom R, Fiol M, Fountain N, Fox K, French J, Freyer Karn C, Friedman D, Geller E, Glauser T, Glynn S, Haas K, Haut S, Hayward J, Helmers S, Joshi S, Kanner A, Kirsch H, Knowlton R, Kossoff E, Kuperman R, Kuzniecky R, Lowenstein D, McGuire S, Motika P, Nesbitt G, **Novotny E,** Ottman R, Paolicchi J, Parent J, Park K, Poduri A, Risch N, Sadleir L, Scheffer I, Shellhaas R, Sherr E, Shih JJ, Shinnar S, Singh R, Sirven J, Smith M, Sullivan J, Thio LL, Venkat A, Vining E, von Allmen G, Weisenberg J, Widdess-Walsh P, Winawer M. The epilepsy phenome/genome project. Clin Trials. 2013 Aug;10(4):568-86.

98. Shain C, Ramgopal S, Fallil Z, Parulkar I, Alongi R, Knowlton R, Poduri A; EPGP Investigators. Polymicrogyria-associated epilepsy: a multicenter phenotypic study from

the Epilepsy Phenome/Genome Project. Epilepsia. 2013 Aug;54(8):1368-75.

99. Epi4K Consortium; Epilepsy Phenome/Genome Project, Allen AS, Berkovic SF, Cossette P, Delanty N, Dlugos D, Eichler EE, Epstein MP, Glauser T, Goldstein DB, Han Y, Heinzen EL, Hitomi Y, Howell KB, Johnson MR, Kuzniecky R, Lowenstein DH, Lu YF, Madou MR, Marson AG, Mefford HC, Esmaeeli Nieh S, O'Brien TJ, Ottman R, Petrovski S, Poduri A, Ruzzo EK, Scheffer IE, Sherr EH, Yuskaitis CJ, Abou-Khalil B, Alldredge BK, Bautista JF, Berkovic SF, Boro A, Cascino GD, Consalvo D, Crumrine P, Devinsky O, Dlugos D, Epstein MP, Fiol M, Fountain NB, French J, Friedman D, Geller EB, Glauser T, Glynn S, Haut SR, Hayward J, Helmers SL, Joshi S, Kanner A, Kirsch HE, Knowlton RC, Kossoff EH, Kuperman R, Kuzniecky R, Lowenstein DH, McGuire SM, Motika PV, **Novotny EJ**, Ottman R, Paolicchi JM, Parent JM, Park K, Poduri A, Scheffer IE, Shellhaas RA, Sherr EH, Shih JJ, Singh R, Sirven J, Smith MC, Sullivan J, Lin Thio L, Venkat A, Vining EP, Von Allmen GK, Weisenberg JL, Widdess-Walsh P, Winawer MR. De novo mutations in epileptic encephalopathies. Nature. 2013 Sep 12;501(7466):217-21 PMID: 23934111 PubMed Central PMCID: PMC3773011

100. Widdess-Walsh P, Dlugos D, Fahlstrom R, Joshi S, Shellhaas R, Boro A, Sullivan J, Geller E; EPGP Investigators. Lennox-Gastaut syndrome of unknown cause: phenotypic characteristics of patients in the Epilepsy Phenome/Genome Project. Epilepsia. 2013 Nov;54(11):1898-904. PMID: 24116958 PubMed Central PMCID:

101. Friedman D, Fahlstrom R; EPGP Investigators. Racial and ethnic differences in epilepsy classification among probands in the Epilepsy Phenome/Genome Project (EPGP). Epilepsy Res. 2013 Dec;107(3):306-10. PMID: 24139856 PubMed Central PMCID: PMC4176610

102. Addis L, Chiang T, Clarke T, Hardison H, Kugler S, Mandelbaum DE, **Novotny E**, Wolf S, Strug LJ, Pal DK. Evidence for linkage of migraine in Rolandic epilepsy to known 1q23 FHM2 and novel 17q22 genetic loci. Genes Brain Behav. 2014 Mar;13(3):333-40. PMID: 24286483 PubMed Central PMCID:

103. EuroEPINOMICS-RES Consortium; Epilepsy Phenome/Genome Project; Epi4K Consortium. De novo mutations in synaptic transmission genes including DNM1 cause epileptic encephalopathies. Am J Hum Genet. 2014 Oct 2;95(4):360-70. PMID: 25262651 PubMed Central PMCID: PMC4185114

104. Lerche H, **Novotny EJ Jr.** Microscopic brain structure revisited in genetic epilepsy. Neurology. 2015 Mar 31;84(13):1290-1. PMID: 25740868

105. Shinnar S, Cnaan A, Hu F, Clark P, Dlugos D, Hirtz DG, Masur D, Mizrahi EM, Moshé SL, Glauser TA; Childhood Absence Epilepsy Study Group. Long-term outcomes of generalized tonic-clonic seizures in a childhood absence epilepsy trial. Neurology. 2015 Sep 29;85(13):1108-14. PMID: 26311751 PubMed Central PMCID: PMC4603882

106. Shurtleff HA, Barry D, Firman T, Warner MH, Aguilar-Estrada RL, Saneto RP, Kuratani JD, Ellenbogen RG, **Novotny EJ**, Ojemann JG. Impact of epilepsy surgery on development of preschool children: identification of a cohort likely to benefit from early intervention. J Neurosurg Pediatr. 2015 Oct;16(4):383-92. PMID: 26140458

107. Epilepsy Phenome/Genome Project Epi4K Consortium. Copy number variant analysis from exome data in 349 patients with epileptic encephalopathy. Ann Neurol. 2015 Aug;78(2):323-8. PMID: 26068938 PubMed Central PMCID: PMC4646089

108. Olson JD, Wander JD, Johnson L, Sarma D, Weaver K, **Novotny EJ**, Ojemann JG, Darvas F. Comparison of subdural and subgaleal recordings of cortical high-gamma activity in humans. Clin Neurophysiol. 2016 Jan;127(1):277-84. PMID: 25907415 PubMed Central PMCID: PMC4600028

109. Mirzaa GM, Campbell CD, Solovieff N, Goold CP, Jansen LA, Menon S, Timms AE, Conti V, Biag JD, Olds C, Boyle EA, Collins S, Ishak G, Poliachik SL, Girisha KM, Yeung KS, Chung BH, Rahikkala E, Gunter SA, McDaniel SS, Macmurdo CF, Bernstein JA, Martin B, Leary RJ, Mahan S, Liu S, Weaver M, Dorschner MO, Jhangiani S, Muzny DM, Boerwinkle E, Gibbs RA, Lupski JR, Shendure J, Saneto RP, **Novotny EJ,** Wilson CJ, Sellers WR, Morrissey MP, Hevner RF, Ojemann JG, Guerrini R, Murphy LO, Winckler W, Dobyns WB. Association of MTOR Mutations With Developmental Brain Disorders, Including Megalencephaly, Focal Cortical Dysplasia, and Pigmentary Mosaicism. JAMA Neurol. 2016 Jul 1;73(7):836-845. PMID: 27159400 PubMed Central PMCID: PMC4979321

110. Casimo K, Darvas F, Wander J, Ko A, Grabowski TJ, **Novotny E,** Poliakov A, Ojemann JG, Weaver KE. Regional Patterns of Cortical Phase Synchrony in the Resting State. Brain Connect. 2016 Jul;6(6):470-81. PMID: 27019319

111. Arya R, Gillespie CW, Cnaan A, Devarajan M, Clark P, Shinnar S, Vinks AA, Mizuno K, Glauser TA; Childhood Absence Epilepsy Study Group.. Obesity and overweight as CAE comorbidities and differential drug response modifiers. Neurology. 2016 Apr 26;86(17):1613-21. PMID: 27029636

112. Buckley RT, Wang AC, Miller JW, **Novotny EJ**, Ojemann JG. Stereotactic laser ablation for hypothalamic and deep intraventricular lesions. Neurosurg Focus. 2016 Oct;41(4):E10. PMID: 27690656

113. Knupp KG, Leister E, Coryell J, Nickels KC, Ryan N, Juarez-Colunga E, Gaillard WD, Mytinger JR, Berg AT, Millichap J, Nordli DR Jr, Joshi S, Shellhaas RA, Loddenkemper T, Dlugos D, Wirrell E, Sullivan J, Hartman AL, Kossoff EH, Grinspan ZM, Hamikawa L; Pediatric Epilepsy Research Consortium. Response to second treatment after initial failed treatment in a multicenter prospective infantile spasms cohort. Epilepsia. 2016 Nov;57(11):1834-1842 PMID: 27615012

114. Cnaan A, Shinnar S, Arya R, Adamson PC, Clark PO, Dlugos D, Hirtz DG, Masur D, Glauser TA; Childhood Absence Epilepsy Study Group. Second monotherapy in childhood absence epilepsy. Neurology. 2017 Jan 10;88(2):182-190. PMID: 27986874

115. EuroEPINOMICS-RES Consortium. Electronic address: euroepinomics-RES@ua.ac.be.; Epilepsy Phenome/Genome Project.; Epi4K Consortium.; EuroEPINOMICS-RES Consortium. De Novo Mutations in Synaptic Transmission Genes Including DNM1 Cause Epileptic Encephalopathies. Am J Hum Genet. 2017 Jan 5;100(1):179. PMID: 28061363

116. Epi4K Consortium; EuroEPINOMICS-RES Consortium; Epilepsy Phenome Genome Project. Application of rare variant transmission disequilibrium tests to epileptic encephalopathy trio sequence data. Eur J Hum Genet. 2017 Jun;25(7):894-899. PMID: 28513609

117. Shinnar RC, Shinnar S, Cnaan A, Clark P, Dlugos D, Hirtz DG, Hu F, Liu C, Masur D, Weiss EF, Glauser TA; Childhood Absence Epilepsy Study Group. Pretreatment behavior and subsequent medication effects in childhood absence epilepsy. Neurology. 2017 Oct 17;89(16):1698-1706. PMID: 28916534

118. **Novotny EJ Jr**. Early genetic testing for neonatal epilepsy: When, why, and how? Neurology. 2017 Aug 29: 89(9):880-881.

119. Berg AT, Coryell J, Saneto RP, Grinspan ZM, Alexander JJ, Kekis M, Sullivan JE, Wirrell EC, Shellhaas RA, Mytinger JR, Gaillard WD, Kossoff EH, Valencia I, Knupp KG, Wusthoff C, Keator C, Dobyns WB, Ryan N, Loddenkemper T, Chu CJ, **Novotny EJ Jr**, Koh S. Early-Life Epilepsies and the Emerging Role of Genetic Testing. JAMA Pediatr. 2017 Jul 31

120. Epi4K consortium; Epilepsy Phenome/Genome Project. Ultra-rare genetic variation in common epilepsies: a case-control sequencing study. Lancet Neurol. 2017 Feb;16(2):135-143. PMID: 28102150

121. Wang AC, Ibrahim GM, Poliakov AV, Wang PI, Fallah A, Mathern GW, Buckley RT, Collins K, Weil AG, Shurtleff HA, Warner MH, Perez FA, Shaw DW, Wright JN, Saneto RP, **Novotny EJ**, Lee A, Browd SR, Ojemann JG. Corticospinal tract atrophy and motor fMRI predict motor preservation after functional cerebral hemispherectomy. J Neurosurg Pediatr. 2018 Jan;21(1):81-89. PMID: 29099351

122. Weaver KE, Poliakov A, **Novotny EJ,** Olson JD, Grabowski TJ, Ojemann JG. Electrocorticography and the early maturation of high-frequency suppression within the default mode network. J Neurosurg Pediatr. 2018 Feb;21(2):133-140. PMID: 29099351

123. Grinspan ZM, Shellhaas RA, Coryell J, Sullivan JE, Wirrell EC, Mytinger JR, Gaillard WD, Kossoff EH, Valencia I, Knupp KG, Wusthoff C, Keator C, Ryan N, Loddenkemper T, Chu CJ, **Novotny EJ Jr**, Millichap J, Berg AT. Comparative Effectiveness of Levetiracetam vs Phenobarbital for Infantile Epilepsy. JAMA Pediatr. 2018 Feb 12. PMID: 29435578

124. Sánchez Fernández I, Gaínza-Lein M, Abend NS, Anderson AE, Arya R, Brenton JN, Carpenter JL, Chapman KE, Clark J, Gaillard WD, Glauser TA, Goldstein JL, Goodkin HP, Helseth AR, Jackson MC, Kapur K, Lai YC, McDonough TL, Mikati MA, Nayak A, Peariso K, Riviello JJ Jr, Tasker RC, Tchapyjnikov D, Topjian AA, Wainwright MS, Wilfong A, Williams K, Loddenkemper T; Pediatric Status Epilepticus Research Group (pSERG). Factors associated with treatment delays in pediatric refractory convulsive status epilepticus. Neurology. 2018 May 8;90(19):e1692-e1701. PMID: 29643084

125. Grassia F, Poliakov AV, Poliachik SL, Casimo K, Friedman SD, Shurtleff H, Giussani C, **Novotny EJ,** Ojemann JG, Hauptman JS. Changes in resting-state connectivity in pediatric temporal lobe epilepsy. J Neurosurg Pediatr. 2018 Aug;22(2):214-219. PMID:

29932365

126. Coryell J, Gaillard WD, Shellhaas RA, Grinspan ZM, Wirrell EC, Knupp KG, Wusthoff CJ, Keator C, Sullivan JE, Loddenkemper T, Patel A, Chu CJ, Massey S, **Novotny EJ Jr**, Saneto RP, Berg AT. Neuroimaging of Early Life Epilepsy. Pediatrics. 2018 Sep;142(3) PMID: 30089657

127. Kuo CH, Feroze AH, Poliachik SL, Hauptman JS, **Novotny EJ Jr,** Ojemann JG. Laser Ablation Therapy for Pediatric Patients with Intracranial Lesions in Eloquent Areas. World Neurosurg. 2019 Jan;121:e191-e199. PMID: 30261370

128. Bozarth X, Dines JN, Cong Q, Mirzaa GM, Foss K, Lawrence Merritt J 2nd, Thies J, Mefford HC, **Novotny E.** Expanding clinical phenotype in CACNA1C related disorders: From neonatal onset severe epileptic encephalopathy to late-onset epilepsy. Am J Med Genet A. 2018 Dec;176(12):2733-2739. PMID: 30513141

129. Bozarth XL, McGuire J, **Novotny E.** Current Status of Continuous Electroencephalographic Monitoring in Critically Ill Children. Pediatr Neurol. 2019 Dec;101:11-17. doi: 10.1016/j.pediatrneurol.2019.07.012. Epub 2019 Aug 2. Review. PubMed PMID: 31493974.

130. Sánchez Fernández I, Gaínza-Lein M, Abend NS, Amengual-Gual M, Anderson A, Arya R, Brenton JN, Carpenter JL, Chapman KE, Clark J, Farias-Moeller R, Davis Gaillard W, Glauser TA, Goldstein J, Goodkin HP, Guerriero RM, Hecox K, Jackson M, Kapur K, Kelley SA, Kossoff EHW, Lai YC, McDonough TL, Mikati MA, Morgan LA, **Novotny EJ,** Ostendorf AP, Payne ET, Peariso K, Piantino J, Riviello JJ Jr, Sannagowdara K, Stafstrom CE, Tasker RC, Tchapyjnikov D, Topjian AA, Vasquez A, Wainwright MS, Wilfong A, Williams K, Loddenkemper T. The onset of pediatric refractory status epilepticus is not distributed uniformly during the day. Seizure. 2019 Aug;70:90-96. doi: 10.1016/j.seizure.2019.06.017. Epub 2019 Jun 18. PubMed PMID: 31323566.

Book Chapters:

1. Wallace DC, Singh, Hopkins LC, **Novotny EJ**. Maternally Inherited Diseases in Man. In: Achievements and Perspectives of Mitochondrial Research Vol. II: Biogenesis. Quagliariello E et al. (eds) Elsevier Science Publishers, Amsterdam. 1985:427-436.
2. **Novotny EJ**. Hypoxic-Ischemic Encephalopathy. In: Fetal and Neonatal Brain Injury: Mechanisms, Management, and the Risk of Malpractice. Stevenson, DK and Sunshine, P. (eds) B. C. Decker, Inc. Philadelphia (1989) Chapt 10, 113-122.
3. **Novotny EJ**. Hereditary Secondary Dystonias. In: Handbook of Clinical Neurology, Vol 15 (59): Diseases of the Motor System. Vinken PJ, Gruyn GW, Klawans HL, de Jong JMBV (eds). Elsevier Science Publishers B.V., Amsterdam, (1991) Chapt 20, 339-349.
4. Laxer KD, Rowley HA, **Novotny EJ**, Gates JR, Sato S, Sutherling W, Elger CE, Ebersole JS, Stefan H. Experimental Technologies. In: Surgical Treatment of Epilepsies. Engel J (ed). Raven Press, New York, (1993) Chapt 23, 291-308.
5. Kain Z, **Novotny EJ**, Lister G. Case 4. In: Case Studies in Pediatric Intensive Care. Rogers 888MC, Helfaer MA. (eds). Williams and Wilkens, Baltimore. (1993) 21-28.
6. Gruetter R, **Novotny EJ**, Boulware SD, Rothman DL, Mason GF, Shulman GI, Tamborlane WV, Shulman RG. Non-invasive Measurements of the Cerebral Steady State

Glucose Concentration and Transport in Humans by ^{13}C Nuclear Magnetic Resonance. In: Frontiers in Cerebral Vascular Biology: Transport and its Regulation. Drewes LR, Betz AL (eds) Plenum Press, New York. 1993, 35-40.

7. **Novotny EJ**. Neonatal Seizures. In: Principles and Practice of Pediatrics. Oski FA, DeAngelis CD, Feigin RD, McMillan JA, Warshaw JB (eds). Second Edition. J. B. Lippincott, Inc. Philadelphia 1994, 357-362.
13. **Novotny EJ.** Cerebral Blood Flow and Metabolism in Hypoxia. In: Tissue Oxygen Deprivation: From Molecular to Integrated function. Haddad GG, Lister G, L'Enfant C (eds) Marcel Dekker, New York 1996, 653-668.
14. Anderson GM, **Novotny EJ**, Shaywitz BA. Evaluation of Seizures. In: The Clinical Evaluation of a Food Additive: Assessment of Aspartame. Tschanz C, Butchko HH, Stargel WW, Kotsonis FN (eds). CRC Press, New York 1996, 205-216.
15. **Novotny EJ**. Neonatal Seizures. In: Principles and Practice of Pediatrics. Oski FA, DeAngelis CD, Feigin RD, McMillan JA, Warshaw JB (eds). Second Edition. J. B. Lippincott, Inc. Philadelphia 1999, 240-245.
16. **Novotny EJ,** Rothman D, Tamborlane W Hypoglycaemia and the child's brain In: Genetic Insights in Paediatric Endocrinology and Metabolism. O'Rahilly S and Dunger DB (eds). BioScientifica, Ltd. Bristol, UK 1999, 31-39.
17. Spencer SS, **Novotny E**, de Lanerolle N, Kim J. Mesial temporal sclerosis: electroclinical and pathological correlations and applications to limbic epilepsy in childhood. In Limbic Seizures in Children, G. Avanzini, A. Beaumanoir & L. Mira (eds.) John Libbey & Company, Ltd. London, UK. 2001 pp 41-54
18. **Novotny EJ**. Neonatal Seizures. In: Principles and Practice of Pediatrics. DeAngelis CD, Feigin RD, McMillan JA, Jones MD (eds). Fourth Edition. J. B. Lippincott, Inc. Philadelphia 2006, Chapt 36, pp 286 – 291.
19. Pearl PL, Acost MT, Theodore WH, **Novotny EJ,** Bennett HD, Jakobs C, Gibson KM. Human SSADH Deficiency – Phenotype and Treatment Strategies. In Diseases of Neurotransmission: from bench to bedside. Hoffman GF (ed). SPS Verlagsgesellschaft Heilbronn 2006, 187 – 198.
20. **Novotny EJ**. What Can Neuroimaging Tell Us?. In: Epilepsy. Neurology in Practice. Miller JW and Goodkin HP (eds). Wiley-Blackwell. 2014, 54 – 60.

Electronic Publications:

1. Rothman DL, **Novotny EJ.** MRS Studies of the role of the glutamate neurotransmitter cycle in the cerebral cortex response to hypoglycemia http://www.jdrf.org/research/workshop090800.pdf. 2001 p 23.
2. **Novotny EJ,** Rothman DL, Tamborlane WV. Relation of hypoglycemia to epileptogenesis. http://www.jdrf.org/research/workshop090800.pdf. 2001 p 30.
3. Pharmaceutical Journal - http://www.pharmaceutical-journal.com/news-and-analysis/features/cannabis-for-epilepsy-is-there-enough-evidence-of-efficacy/20202138.article

Abstracts (pre-1990):

1. Sogg RL, Steinman LS, **Novotny EJ**. Childhood Myasthenia. Presented at the meeting of the Fourth International Congress of Neuro-ophthalmology in Hamilton, Bermuda on

June 14, 1982.

2. **Novotny EJ**, Sogg RL, Steinman LS. Myasthenia Gravis in Prepubertal Children. Read at the Child Neurology Society Meeting in Salt Lake City, Utah in October, 1982.
3. **Novotny EJ**, Tharp BR, Steinman LS, et al. A Myoencephalopathy associated with Leber's Optic Neuropathy with Nonmendelian Inheritance. Presented at the 36th annual meeting of the American Academy of Neurology in Boston, MA on April 12, 1984. Neurology 34 (Suppl 1):273, 1984.
4. Sogg RL, **Novotny EJ**. A Myoencephalopathy associated with Leber's Optic Neuropathy with Nonmendelian Inheritance (Neuro-ophthalmological features). Presented at the Meeting of the Fifth International Congress of Neuro-ophthalmology in Antwerp, Belgium on May 17, 1984.
5. Sogg RL, **Novotny EJ**. Congenital Arthrogryposis Multiplex. Presented at the 17th Annual Frank B. Walsh Society Meeting in Baltimore, Maryland on February 23, 1985.
6. **Novotny EJ**, Wallace DC, Singh G, et al. A Neurodegenerative Disorder with Generalized Dystonia: A New Mitochondriopathy? Presented at the 37th annual meeting of the American Academy of Neurology in Dallas, TX on May 1, 1985. Neurology 1985;35 (Suppl 1):273.
7. Coen R, Bejar R, **Novotny EJ**, et al. A Characteristic EEG Pattern in Multifocal Cerebral White Matter Necrosis. Presented at the American Pediatric Society meeting in Washington, D.C. on May 17, 1985.
8. Wallace DC, Singh G, Hopkins LC, **Novotny EJ**. Maternally Inherited Diseases of Man. Presented in September, 1985 in Bandizzi, Italy.
9. **Novotny EJ**, Coen R, Tharp BR, Bejar R and Enzmann D. The Significance of Positive Sharp Sharp Waves in the Electroencephalogram of the Premature Infant. Presented at the 38th annual meeting of the Academy of Neurology in New Orleans on May 1, 1986. Neurology 1986;36(Suppl 1):279.
10. Young RSK, Cowan BE, **Novotny EJ**, and Sena M. How does hypoglycemia affect brain energy metabolism during prolonged neonatal seizures? Ann Neurol 1986;20:434.
11. **Novotny EJ**, Young RSK, Lotspeich L, and Smith D. Cerebellar infarction in childhood: clinical and neuropathological findings. Read at the 15th annual meeting of the Child Neurology Society in Boston, MA in October, 1986.
12. Weinstein S, **Novotny EJ**. Neonatal Metabolic disorders Masquerading As Structural Central Nervous System Anomalies. Ann Neurol 1987;22:406.
13. **Novotny EJ**, Ogino T, Petroff OAC, Prichard JW, Shulman RG. In vivo Metabolism of 2-13C-Ethanol in the Rabbit Brain by Combined Heteronuclear and Homonuclear Editing. Seventh Annual Meeting, Society of Magnetic Resonance in Medicine, August, 1988.
14. Ogino T, **Novotny EJ**, Petroff OAC, Prichard JW, Rothman DL, Shulman RG. Approaching perfection in an imperfect system: determination of relaxation times in vivo. Seventh Annual Meeting, Society of Magnetic Resonance in Medicine, August, 1988.
15. Hanstock C, Rothman DL, Shulman R, **Novotny E**, Petroff O, Prichard J. Ethanol observed in human brain by proton magnetic resonance spectroscopy. Seventh Annual Meeting, Society of Magnetic Resonance in Medicine, August, 1988.
16. Avison MJ, Herskowitz N, **Novotny EJ**, Petroff OAC, Rothman DL, Shulman RG, Prichard JW. Measurement of Cerebral Phenylalanine Concentration in a Rabbit Model

of Hyperphenylalanemia. Seventh Annual Meeting, Society of Magnetic Resonance in Medicine, August, 1988.

17. **Novotny EJ**, Avison MJ, Rothman DL, Seashore MR, Petroff OAC, Herschkowitz N, Prichard JW, and Shulman RG. Detection of phenylalanine in the human brain. Eighth annual meeting of the Society of Magnetic Resonance in Medicine (1989), 441.
18. **Novotny EJ**, Rothman DL, Avison MJ, Petroff OAC, Lantos GL, Prichard JW, and Shulman RG. Determination of cerebral metabolic rates in vivo using 1-13C-glucose. Eighth annual meeting of the Society of Magnetic Resonance in Medicine (1989), 336.
19. Rothman DL, **Novotny EJ**, Howseman A, Petroff OAC, Lantos GL, Hanstock CC, Shulman GI, Prichard JW, and Shulman RG. ^{1}H NMR measurement of 4-^{13}C-glutamate turnover in the human brain. Eighth annual meeting of the Society of Magnetic Resonance in Medicine (1989), 1060.
20. Rothman DL, Howseman A, **Novotny EJ**, Hanstock CC, Lantos GL, Petroff OACP, Prichard JW, and Shulman RG. Feasibility of proton-observe carbon-decouple editing of glutamate in the human brain. Eighth annual meeting of the Society of Magnetic Resonance in Medicine (1989), 372.
21. Hanstock CC, Rothman DL, Howseman A, **Novotny EJ**, Lantos GL, Petroff OACP, Prichard JW, and Shulman RG. In vivo determination of NAA concentration in the human brain using the proton aspartyl resonance. Eighth annual meeting of the Society of Magnetic Resonance in Medicine (1989), 442.
22. Petroff OAC, **Novotny EJ**, Rothman DL, Avison MJ, Prichard JW, and Shulman RG. Cerebral lactate turnover after electroshock by proton-observe carbon-decouple spectroscopy. Eighth annual meeting of the Society of Magnetic Resonance in Medicine (1989), 332.
23. Prichard JW, Rothman DL, **Novotny EJ**, Petroff OAC, Avison MJ, Howseman A, Hanstock CC, and Shulman RG. Photic stimulation raises lactate in human visual cortex. Eighth annual meeting of the Society of Magnetic Resonance in Medicine (1989), 1071.
24. **Novotny EJ**, Rothman DL, Avison MJ, Petroff OAC, Lantos G, Prichard JW, Shulman RG. Determination of Cerebral Metabolic Rates *In Vivo* using Stable Isotopically Labeled Glucose. Ann Neurol 1989;26:43.
25. **Novotny EJ**, Petroff OAC, Graham G, Shulman RG, Prichard JW. Quantification of Lactate in the Rabbit Brain in Situ. Abstracts of the Society of Magnetic Resonance in

PUBLICATIONS:

Abstracts (1993 – present) :

1. **Novotny EJ**, R. Gruetter, D. L. Rothman, S. Boulware, W.V. Tamborlane, R.G. Shulman. CHRONIC HYPERGLYCEMIA DOES NOT ALTER STEADY-STATE HUMAN BRAIN GLUCOSE CONCENTRATIONS. A ^{13}C NMR STUDY. Abstracts Child Neurology Society Meeting, **Ann Neurol**, 1993:34;467.
2. **Novotny EJ**, Graeme F. Mason, Rolf Gruetter, Douglas Rothman, Kevin L Behar, Robert G. Shulman. DETERMINATION OF THE KREBS CYCLE RATE IN HUMAN BRAIN

IN VIVO BY ^{13}C NMR SPECTROSCOPY. Abstracts Child Neurology Society Meeting, **Ann Neurol**, 1993:34;467.

3. **Novotny EJ**, Chen W, Rothman DL, Shulman RG. LOCALIZED ^{1}H NMR MEASUREMENT OF GLUCOSE CONSUMPTION IN THE HUMAN BRAIN DURING VISUAL STIMULATION. Abstracts Child Neurology Society Meeting, **Ann Neurol**, 1993:34;448.
4. Masuoka LK, Anderson AW, Gore JC, McCarthy G, **Novotny EJ**. Activation of visual cortex in occipital lobe epilepsy using functional magnetic resonance imaging. Abstracts American Epilepsy Society, **Epilepsia** 35 (Suppl 8):86, 1994
5. **Novotny EJ**, Masuoka LK, Anderson AW, Gore JC, McCarthy G, Spencer D. Functional magnetic resonance imaging (fMRI) in Pediatric Epilepsy. Abstracts American Epilepsy Society, **Epilepsia** 35 (Suppl 8):36, 1994.
6. Berg AT, Shinnar S, **Novotny EJ**. Intractable Epilepsy in Childhood. Abstracts American Epilepsy Society, 1994.
7. Levy S, Testa F, Chiappa KH, **Novotny EJ**, Berg AT. Comparison of Digital and conventional Electroencephalogram (EEG) Interpretation. Abstracts American Epilepsy Society, 1994.
8. Chen W, **Novotny EJ**, Boulware SD, Rothman DL, Mason GF, Zhu X.-H, Blamire A, Prichard JW, Shulman RG. Quantitative measurements of regional TCA cycle flux in visual cortex of human brain using ^{1}H-{^{13}C} NMR spectroscopy. Abstracts Society of Magnetic Resonance, 1994.
9. Chen W, **Novotny EJ**, Rothman DL, Shulman RG. Simultaneous measurements of regional C4 glutamate from two localized volumes in human brain using ^{1}H-{^{13}C} NMR spectroscopy. Abstracts Society of Magnetic Resonance, 1994.
10. **Novotny EJ**, Ariyan C, Rothman DL, Haddad GG, Mason G, Lai JC, Behar KL. NMR Spectroscopic Studies of the Ontogeny of Cerebral Glucose Metabolism in the Rat. SMR Workshop on Advances in Physiological Chemistry by In Vivo NMR. Woods Hole, MA, March, 1995.
11. **Novotny EJ**, Mason GF, Gruetter R, Rothman D, Chen W, Behar KL, Prichard J, Boulware S, Zhu X-H, Shulman RG. Determination of Krebs cycle, glutamine synthesis and amino acid turnover in vivo by 13C NMR spectroscopy. International Society for Neurochemistry , **J Neurochem** 1995;65(Suppl):S206.
12. **Novotny EJ**, **Ariyan C, Rothman DL, Haddad GG, Mason G, Lai JC, Behar KL.** NMR Spectroscopic Studies of the Ontogeny of Cerebral Glucose Metabolism in the Rat. Society of Magnetic Resonance, 1995.
13. **Novotny EJ**, Ariyan C, Behar KL. Adaptive mechanisms in developing brain: III. Metabolism. Ann Neurol 1995;38:533.
14. Ment LR, Haddad GG, Madri JA, **Novotny EJ**, Schwartz ML, Stewart WB. Adaptive mechanisms in developing brain: I. Neuropathology. **Ann Neurol** 1995;38:521.
15. **Novotny EJ**, Ariyan C, Akiyama*Y, O'Reilly J P, Behar KL, Haddad GG**.** Comparison of the ontogeny of brain oxidative metabolism *in vivo* vs *in vitro*: an NMR spectroscopic study. Society for Neuroscience, 25th Annual Meeting, San Diego, CA 1995.
16. **Novotny EJ,** Rothman DL, Assaf B. Cerebral amino acid levels in childhood genetic epilepsies. Neurology 46(2 (Suppl)): A166, 1996**.**

17. Assaf BA, Rothman DL, **Novotny EJ.** Cerebral amino acid levels in juvenile myoclonic epilepsy. Neurology 46(2 (Suppl)): A446, 1996.
18. **Novotny EJ**, Rothman DL. Altered amino acid levels in pediatrics epilepsies. International Society for Magnetic Resonance in Medicine. Fourth Scientific Meeting. New York, NY. April, 1996. p. 132.
19. Rothman DL, Behar KL, Mattson RH, Prichard JW, **Novotny EJ**, Petroff OAC. Homocarnosine levels are elevated in epileptic patients taking vigabatrin: a novel measure of cortical pH. International Society for Magnetic Resonance in Medicine. Fourth Scientific Meeting. New York, NY. April, 1996. p. 130.
20. **Novotny EJ**, Matalon R, Hwang J-H, Rothman DL. Brain amino acids in aspartoacylase II deficiency. International Society for Magnetic Resonance in Medicine. Fourth Scientific Meeting. New York, NY. April, 1996. p. 311.
21. Assaf B, Rothman DL, Mattson RH, **Novotny EJ**. Cerebral GABA levels in sporadic and familial juvenile myoclonic epilepsy. International Society for Magnetic Resonance in Medicine. Fourth Scientific Meeting. New York, NY. April, 1996. p. 963
22. N**ovotny EJ**, Rothman DL. Observation of Cerebral Ketone Bodies by Proton NMR Spectroscopy. Ann Neurol, 40:285, 1996.
23. **Epstein RW,** Anderson AW, Novotny EJ, Skudlarski P, Gore JC. Asymmetries in visual function in occipital lobe epilepsy: Detection with functional MR imaging. RADIOLOGY 201: 24-24, Suppl. S NOV 1996
24. **Novotny EJ**, Rothman DL. Cerebral Glutamate and γ-aminobutyric Acid in Pediatric Epilepsy.
25. **Novotny EJ**, Chen J, Rothman DL. Alterations in cerebral metabolism with the ketogenic diet. Epilepsia, 38:147, 1997.
26. Hyder F, Rothman DL, Shevell M, **Novotny EJ.** Cerebral GABA in pediatric epilepsy. Epilepsia, 38:127-8, 1997.
27. Varelas P, Cardoza C, **Novotny EJ**, Levy SL, Testa F. Diagnostic utility of long-term video/EEG monitoring in children. Epilepsia, 38 (suppl 8) : 220, 1997.
28. Bronen RA, Fulbright RK, Spencer SS, Kim JH, Spencer DD, Novotny EJ Balloon cell focal cortical dysplasia of Taylor: A forme fruste of tuberous sclerosis? Radiology 205: 773-773, Suppl. 1997
29. Pavlakis SG, **Novotny EJ**, Hyder F, Rothman D Brain gamma-aminobutyric acid glutamate in pyridoxine-dependent seizures Ann Neurol, 44:B19, 1998
30. **Novotny EJ**, Hyder F, Behar KL, Petroff OAC, Rothman DL. Alterations in Cerebral GABA and Glutamate in Human epilepsy. Society for Neuroscience Abstracts, 23:816, 1997.
31. **Novotny EJ**, Hyder F, Mason G, Rothman DL. Cerebral GABA in Childhood Generalized Epilepsy. Society for Neuroscience Abstracts, 25:602, 1999.
32. **Novotny EJ**, Hyder F, Mason G, Rothman DL. Cerebral GABA in Childhood Generalized Epilepsy. American Epilepsy Society Proceedings. Epilepsia 1999 40 (Suppl 7): 125
33. **Buerstatte CR, Behar KL, Novotny EJ, White BK, Lai JCK** Chronic postnatal hypoxia selectively decreases KGDHC activities in rat brain regions. FASEB J. 13: (5) A1100-A1100, Part 2, Suppl. S MAR 15 1999
34. **Novotny EJ**, Hyder F, Mason G, Rothman DL. Cerebral GABA in Pediatric Epilepsy. Abstracts of Pediatric Academic Society Meeting May 2000.

35. Studholme C, **Novotny E,** Stokking R, Duncan JS, Zubal IG, Spencer D. Alignment of Functional Data Acquired Before And After Intra-Cranial Electrode Implantation Using Non-Rigid Anatomical MRI Registration. International Society for Magnetic Resonance in Medicine. Eighth Scientific Meeting. Denver Apr 2000 p585.
36. **Novotny EJ**, Hyder F, Mason G, Rothman DL. **Observation of valproic acid in human brain by proton MRS.** Epilepsia 2000; 41 (Suppl 7): .
37. Teague B, Wilson KG, **Novotny EJ.** Behavioral training in a mock scanner improves success of diagnostic imaging in pediatric epilepsy patients. Abstract #3.231 Epilepsia 2000; 41 (Suppl 7):
38. I. Kida; F. Hyder; **E.J. Novotny**, W. Abi-Saab; K.L. Behar. Voltage-gated sodium channels and glutamate release underlie bold functional MRI response to forepaw stimulation in the rat. Society for Neuroscience Abstracts, 136.1, 2000
39. **Novotny EJ**, Bara-Jiminez W, Hallett M, Pagan F, Boudreau F, Mason G, and Rothman DL **Cerebral GABA in Lafora disease** Society for Neuroscience Abstracts, 2001.
40. White BK, Buerstatte CR, Behar KL, **Novotny EJ**. Differential effects of chronic hypoxia on glycolytic and tricarboxylic acid cycle enzymes in developing brain FASEB J 15 (4): A562-A562 Part 1 MAR 7 2001
41. Singh SP, **Novotny EJ**, Nguyen DK, Thompson J, Spencer D, Spencer S. Surgical outcome in frontal lobe epilepsy: On the basis of pathology and region NEUROLOGY 58 (7): A51-A51 Suppl. 3 APR 9 2002
42. Hal Blumenfeld MD, PhD, Susan Vanderhill, LeBron Paige MD, Maria Corsi, **Edward J. Novotny, Jr. MD**, I. George Zubal PhD and Susan S. Spencer MD. IMAGING CORTICAL AND SUBCORTICAL NETWORKS IN HUMAN TEMPORAL LOBE SEIZURES. Epilepsia 43 (Suppl 7) 310, 2002
43. Gibson KM, Gupta M, Callan M, Senephansiri H, Polinsky M, Grompe M, **Novotny EJ**, Pearl P, Jansen EEW, Bakkali A, Jakobs C. Abnormal GABA/glutamine metabolism in succinic semialdehyde dehydrogenase (SSADH) deficiency, an epilepsy syndrome with elevated CNS. AMERICAN JOURNAL OF HUMAN GENETICS 2002; 71 Suppl. S (4): 52
44. Trübel H, Herman P, Maciejewski P, **Novotny EJ**, Hyder F. Selective brain cooling: temperature changes during hypercapnia and seizure activity. Brain 03 XXIst Meeting International Society for Cerebral Blood Flow and Metabolism 7/1/2003, Calgary, CA
45. Pearl PL, **Novotny EJ,** Acosta MT, Jakobs C, Gibson KM. Clinical and Metabolic Investigations Offer New Insights into Pathophysiology of SSADH Deficiency. Child Neurology Society 10/4/2003, Miami, FL, ANN NEUROL 2003;54(Suppl. 7): S107-S107.
46. **Novotny EJ**, de Graaf R, Mason G, Appel M, Gibson KM, Pearl P, and Rothman DL. Brain GABA in SSADH deficiency Child Neurology Society 10/4/2003, Miami, FL, ANN NEUROL 2003;54(Suppl. 7): S106-S107
47. McNally, KA, Vanderhill, S, Paige AL, Doernberg S, Chung R, Adamiak K, **Novotny EJ**, Zubal, IJ, Spencer S, Blumenfeld H. EXCITATORY AND INHIBITORY NETWORK INTERACTIONS DURING LOSS OF CONSCIOUSNESS IN TEMPORAL LOBE EPILEPSY. American Epilepsy Society, Boston, MA 12/2003
48. Acosta MT, Pearl PL, Novotny EJ, and Gibson KM **Role of GABA in Autism: New Clues from Hyper-GABAergic States** Child Neurology Society 10/13/2004 Ann Neurol

2004;56 (S8): S103

49. Pearl PL, Acosta MT, Bottiglieri T, Miotto K., Novotny EJ, and Gibson KM. **Movement Disorders in SSADH Deficiency:More Severe Phenotype and Relevance to GHB Toxicity** Child Neurology Society 10/13/2004 Ann Neurol 2004;56 (S8): S120
50. Hisama FM, Fertig EF, Hariri A, Bockenhauer D, Lifton RP, [1]Spencer SS, and **Novotny EJ** FAMILIAL PRIMARY HYPOMAGNESEMIA AND TEMPORAL LOBE EPILEPSY Epilepsia 45 Suppl. 7 :223 (Abst. 2.091) , 2004
51. Paige AL, McNally K, Zubal IG, **Novotny EJ,** Spencer SS, and Blumenfeld H IMPORTANTCE OF TRUE ICTAL SPECT IN LOCALIZING TEMPORAL AND EXTRA-TEMPORAL EPILEPSY Epilepsia 45 Suppl. 7 :304 (Abst. 2.334) , 2004
52. Negishi M, Blumenfeld H, **Novotny EJ**, Spencer DD, and Constable RT A COMBINED EEG (ELECTROENCEPHALOGRAPHY) REFERENCE METHOD FOR SIMULTANEOUS EEG-FMRI (FUNCTIONAL MAGNETIC RESONANCE IMAGING) RECORDING OF EPILEPSY Epilepsia 45 Suppl. 7 :303 (Abst. 2.332) , 2004
53. **E.J. Novotny**, E. Scharff, H. Zaveri, H. Blumenfeld, X. Papademetris, S.S. Spencer, D.D. Spencer, R.B. Duckrow, H.P. Hetherington, J. Duncan. CORRELATION OF MAGNETIC RESONANCE SPECTROSCOPIC IMAGING AND INTRACRANIAL EEG RECORDING IN LATERALIZATION OF EPILEPSY Program No. 132.5. *2005 Abstract Viewer/Itinerary Planner.* Washington, DC: Society for Neuroscience, 2005. Online.
54. R. Berman, M. Negishi, R. Constable, **E. Novotny**, S. Levy, H. Blumenfeld. SIMULTANEOUS EEG AND FMRI RECORDINGS OF CHILDHOOD ABSENCE SEIZURES Program No. 876.2. *2005 Abstract Viewer/Itinerary Planner.* Washington, DC: Society for Neuroscience, 2005. Online.
55. Negishi M, **Novotny EJ**, Blumenfeld H, Spencer SS, Spencer DD, Constable RT. Investigation of the radio-frequency (RF) pulse artifact in simultaneous electroencephalogram-functional magnetic resonance imaging (EEG-fMRI) recording. EPILEPSIA 46: 56-56 Suppl. 8, 2005.
56. Scharff E, Zaveri H, Papademetris X, Blumenfeld H, Duckrow RB, Hetherington HP, Spencer SS, Spencer DD, Duncan J, **Novotny EJ.** Correlation of magnetic resonance spectroscopic imaging and intracranial EEG localization of seizures. EPILEPSIA 46: 56-57 Suppl. 8, 2005.
57. Shetty-Alva N, **Novotny EJ**, Shetty T, Kuo PH. Serial ictal F-18FDG-PET imaging in Rasmussen's encephalitis. NEUROLOGY 66 (5): 267-267 Suppl. 2, MAR 14 2006
58. Durazzo, Tyler S., Duckrow, Robert B., **Novotny, Edward J**., Spencer, Susan S., Zaveri, Hitten P. Circadian patterns of intracranial seizures arising from various epileptogenic regions. EPILEPSIA 47: 30-30 Suppl. 4, 2006
59. Goncharova, Irina I., Zaveri, Hitten P., **Novotny, Edward J.**, Duckrow, Robert B., Spencer, Susan S. Interictal activity recorded intracranially during wakefulness and sleep differentiates patients with medial temporal and temporal neocortical onset of seizures. EPILEPSIA 47: 31-31 Suppl. 4, 2006
60. Negishi, Michiro, Blumenfeld, Hal, **Novotny, Edward J.,** Fertig, Evan, Spencer, Dennis D., Spencer, Susan S., Constable, R. Todd. Spectral analysis of interictal fMRI data. EPILEPSIA 47: 90-91 Suppl. 4, 2006

61. Berman, Rachel), Negishi, Michiro, Spann, Marissa, Enev, Miro, Constable, R. Todd, **Novotny, Edward J.**, Blumenfeld, Hal. Combined EEG, FMRI, and cognitive testing during typical childhood absence seizures at 3T. EPILEPSIA 47: 131-132 Suppl. 4, 2006
62. Constable, R. Todd, Hetherington, Hoby P., Arora, Jagritia, Schafer, Robin, **Novotny, Edward J.**, Papademetris, Xenios, Duncan, James S., Spencer, Dennis D. BOLD MR signal changes in response to cognitive activity are present in cortical regions exhibiting disrupted Cr/NAA ratio. EPILEPSIA 47: 67-67 Suppl. 4, 2006
63. Mason, G. F., Boumezbeur, F., Sanacora, G., Guidone, E., Watzl, J., Gomez, R., **Novotny, E.,** Weinzimer, S., Shulman, G. I., Krystal, J. H., Rothman, D. L., O'Malley, S. Nicotine increases GABA synthesis in human brain, seen with 13C MRS in vivo. ALCOHOLISM-CLINICAL AND EXPERIMENTAL RESEARCH 31 (6): 19A-19A Suppl. S, JUN 2007
64. **Novotny, E**; Negishi, M; Fertig, E, et al. Combined EEG and fMRI in presurgical evaluation of pediatric epilepsy. ANNALS OF NEUROLOGY 62(Suppl 11): S139-S139, 2007.
65. Constable RT, Rajeevan N, Negishi M., Fertig E., Huh L., **Novotny E**., Blumenfeld H., Spencer D. D., Spencer S. S. Resting state FMRI for revealing hemispheric asymmetry in language, memory, and epileptogenic networks in epilepsy . EPILEPSIA 48(Suppl 6): 178-179: 2007
66. Negishi M., Fertig E., Teisseyre T. Z, Huh L., **Novotny E**., Blumenfeld H., Spencer D. D., Spencer, S. S., Constable RT. Comparison of inter-ictal spike correlated FMRI and ictal difference SPECT localization of epilepsy EPILEPSIA 48(Suppl 6): 179-180: 2007
67. Rajeevan N, Negishi M, **Novotny EJ**, Blumenfeld H, Spencer D , Spencer SS, Constable T EVALUATING EPILEPTIC NETWORKS IN SURGICAL PLANNING BY SIMULTANEOUS EEG-FMRI AND FUNCTIONAL CONNECTIVITY EPILEPSIA 49 (Suppl 7): 304-305: 2008.
68. Bai XX , Berman R, Negishi M, **Novotny EJ**, Constable T, Blumenfeld H. FMRI TIMECOURSE AND CORRELATION ANALYSIS IN TYPICAL CHILDHOOD ABSENCE SEIZURES. EPILEPSIA 49(Suppl 7): 405: 2008.
69. Negishi M, Qiu M, **Novotny E J**, Spencer SS, Spencer D, Constable T. EEG-BOLD (BLOOD OXYGEN-LEVEL DEPENDENT) AND EEG-CBV (CEREBRAL BLOOD VOLUME) MEASUREMENTS OF IED'S. EPILEPSIA 49(Suppl 7): 405: 2008.
70. **Novotny E**, Renfroe B, Yardi N, Nordli D, Ness S, Wang S, Weber T, Yuen E, Eerdekens M, Ford L. A randomized, double-blind, placebo-controlled, fixed dose-ranging study to assess the efficacy, safety, and tolerability of topiramate oral liquid and sprinkle formulations as an adjunct to concurrent anticonvulsant therapy for infants (1 to 24 months of age, inclusive) with refractory partial onset seizures. ANNALS OF NEUROLOGY. 64(Suppl 12):S118: 2008
71. Bai X, Killory B, Guo J, Vestal M, Berman R, Negishi M, **Novotny E**, Constable R and Blumenfeld H. Cluster analysis applied to fMRI data in typical childhood absence seizures. Epilepsia 51, 2010
72. **Novotny E**, Poliakov A, Shurtleff H, Warner M, Kuratani J, Saneto R, Shaw D and Ojemann J. Functional connectivity analysis of memory networks in epilepsy.
73. Negishi M, Martuzzi R, **Novotny E**, Spencer D and Constable R. Laterality of the EEG-fMRI seeded functional connectivity as a predictor of the surgical outcome of epilepsy.

Epilepsia 51, 2010

74. Killory B, Bai X, Negishi M, Vega C, Spann M, Vestal M, Berman R, Danielson N, Guo J, Foote S, **Novotny E**, Constable R and Blumenfeld H. Absence seizures impair attention and network connectivity in children. Epilepsia 51, 2010
75. Danielson N, Guo J, Killory B, Bai X, Negishi M, Vestal M, Berman R, Vega C, Spann M, **Novotny E**, Constable R and Blumenfeld H. Ictal BOLD changes and behavioral performance variability in childhood absence epilepsy. Epilepsia 51, 2010
76. Ojemann J, Poliakov A, Shaw D, Saneto R, Kuratani J and **Novotny E**. Diffusion Tensor Imaging (DTI) shows motor fibers may be intimately related to cortical dysplasia. Epilepsia 51, 2010
77. S.L. Poliachik, A.V. Poliakov, Laura Jansen, Sharon McDaniel, Carter Wray, Russ Saneto, John Kuratani, Ojemann J.G**., Novotny E.J. Jr**. Localization of Tissue Removed During Epilepsy Surgery. Epilepsia 52, 2011
78. J. G. Ojemann, A. Poliakov, S. Poliachik, , S. McDaniel, R. Saneto, J. Kuratani, K. Weaver, , C. Wray, H. Shurtleff, M. Warner, D. Shaw, **E. J. Novotny Jr.** Functional connectivity MRI reveals disrupted interhemispheric connectivity in children with diffuse, but lateralized, epilepsy. Epilepsia 52, 2011
79. H. Shurtleff, T. Firman, M. Warner, R. P. Saneto, J. Kuratani, R. Ellenbogen**, E. Novotny**, J. Ojemann. Outcome Following Focal Epilepsy Surgery in Very Young Intact Children. Epilepsia 52, 2011.
80. J. Guo, X. Bai, M. Negishi, N. Danielson, X. Han, J. Gonzalez, E. Loftfield, M. Wang, H. Mistry, R. Berman, C. Vega, M. Spann, **E. Novotny**, R. T. Constable, H. Blumenfeld. EEG and fMRI correlates of ictal task performance during childhood absence seizures. Epilepsia 52, 2011.
81. T. M. Blakely, C. Wray, S. L. Poliachik, A. Poliakov, S. M. McDaniel, **E. J. Novotny**, J. G. Ojemann. Multimodality localization of sensorimotor cortex in pediatric epilepsy surgery. Epilepsia 52, 2011.
82. H. Shurtleff, T. Firman, M. Warner, R. P. Saneto, J. Kuratani, R. Ellenbogen, **E. Novotny,** J. Ojemann. Outcome Following Focal Epilepsy Surgery in Very Young Intact Children. AES 2011
83. J. Guo, X. Bai, M. Negishi, N. Danielson, X. Han, J. Gonzalez, E. Loftfield, M. Wang, H. Mistry, R. Berman, C. Vega, M. Spann**, E. Novotny**, R. T. Constable, H. Blumenfeld. EEG and fMRI correlates of ictal task performance during childhood absence seizures. AES 2011
84. T. M. Blakely, C. Wray, S. L. Poliachik, A. Poliakov, , S. M. McDaniel, E. J. Novotny, J. G. Ojemann, Multimodality localization of sensorimotor cortex in pediatric epilepsy surgery. AES 2011
85. E. J. Novotny, , S. L. Poliachik, , A. V. Poliakov, , L. Jansen, , S. McDaniel, C. Wray, J. Kuratani, R. Saneto, J. Ojemann. Tissue Localization Resected During Epilepsy Surgery
86. C. Wray, R. P. Saneto, E. J. Novotny, J. G. Ojemann. Is post-resective intraoperative electrocorticography predictive of seizure outcomes in children?
87. J. G. Ojemann, A. Poliakov, S. Poliachik, , S. McDaniel, R. Saneto, J. Kuratani, K. Weaver, , C. Wray, H. Shurtleff, M. Warner, D. Shaw, **E. J. Novotny Jr**, Functional connectivity MRI reveals disrupted interhemispheric connectivity in children with diffuse, but lateralized, epilepsy

88. E. Simard-Tremblay, P. Berry, B. Cook, A. Owens, M. Mazzanti, E. Novotny, R. Saneto, HIGH FAT DIET CONTROL OF SEIZURES IN DOOSE SYNDROME. AES 2012
89. K. Weaver, J. G. Ojemann, A. Poliakov, N. Kleinhans, G. Pauley, T. Grabowski, E. Novotny, DECREASED REGIONAL HOMOGENEITY, A MEASURE OF LOCAL FUNCTIONAL CONNECTIVITY, IN INTRACTABLE FOCAL EPILEPSY
90. S. Poliachik, **E. J. Novotny**, A. V. Poliakov, G. E. Ishak, S. S. McDaniel, E. Simard-Tremblay, J. Kuratani, R. Saneto, J. Ojemann, ENHANCED MULTIMODAL IMAGING ASSESSMENT FOR EPILEPSY.
91. R. Gross, J. Willie, S. Helmers, A. Mehta, C. Harden, D. Couture, G. Popli, A. Sharan, M. Sperling, R. Marsh, G. Worrell, G. Cascino, M. Weinand, D. Labiner, S. Danish, S. Wong, R. Wharen, J. Shih, D. Curry, A. Wilfong, J. Ojemann, **E. Novotny,** N. Tandon, STEREOTACTIC LASER AMYGDALOHIPPOCAMPOTOMY FOR MESIAL TEMPORAL LOBE EPILEPSY: RESULTS OF MULTICENTER EXPERIENCE AT 6 MONTHS AND 1 YEAR. AES 2013.
92. Hillary Shurtleff, Jason Nixon, Molly Warner, Andrew Poliakov, Dennis Shaw, Edward Novotny and Jeffrey Ojemann. FMRI MESIAL TEMPORAL ACTIVATION PARADIGM FOR CHILDREN WITH EPILEPSY. AES 2014
93. Andrew Poliakov, **Edward Novotny**, Sandra Poliachik, Seth Friedman, Gisele Ishak, Jason Nixon, Dennis Shaw and Jeff Ojemann. VOXEL-MIRRORED HOMOTOPIC CONNECTIVITY ANALYSIS OF PEDIATRIC EPILEPSY PATIENTS WITH MESIAL TEMPORAL SCLEROSIS
94. Sandra Poliachik, Robert Hevner, **Edward Novotny**, Andrew Poliakov, Gisele Ishak, Hedieh Eslamy, John Kuratani, Russell Saneto and Jeff Ojemann. VOLUME RENDERINGS OF INTRAOPERATIVE ELECTROCORTICOGRAPHY IN EPILEPSY. AES 2014
95. Renee Shellhaas, William D. Gaillard, Tobias Loddenkemper, Anup Patel, Joseph Sullivan, Cynthia Keator, Kelly G. Knupp, Catherine Chu, Zachary Grinspan, Adam Hartman, Courtney Wusthoff, Jason Coryell, Elaine Wirrell, **Edward Novotny,** Ignacio Valencia, Nicole Ryan, Douglas R. Nordli, Carol Camfield, Peter Camfield, Anne Berg. Initial treatment for children <3 years with new-onset epilepsy has changed dramatically from 1977-2015 but remains largely empirical. AES 2015
96. Xiuhua L. Bozarth, Ghayda Mirzaa, Heather Mefford, James Bennettt, Fuki Hisama, William Dobyns, Karen Tsuchiya, Edward Novotny. EPIPX gene panel for epileptic encephalopathy. AES 2015
97. Anne T. Berg, Samya Chakravorty, Sookyong Koh, … Edward J. Novotny, Courtney Wusthoff, Eric Kossoff, Joseph Sullivan, Cynthia Keator. Why West? Comparison of age and etiologic factors in infants who do and do not develop spasms. AES 2017
98. Thomas J. Foutz, Elisabeth Simard-Tremblay, Felix Darvas, Jeffrey G. Ojemann, Edward J. Novotny. Functional Mapping with Surface High-Gamma Frequency EEG in Pediatric Patients. AES 2017
99. Zachary Grinspan, … Edward J. Novotny, John J. Millichap, and Anne T. Berg. Superior Effectiveness of Levetiracetam over Phenobarbital for Infantile Nonsyndromic Epilepsy: A Prospective Multi-Center Observational Study AES 2018
100. Jason Lockrow; Kimberly Foss, Ghayda Mirzaa, Edward J. Novotny, Christopher Beatty. Optimizing Genetic Testing in Epilepsy: The Utility of a Multidisciplinary Epilepsy

Genetics Clinic AES 2018

101. Lindsey Morgan Christopher Beatty Leslie Dervan, Lorie Hamiwka, Jennifer Hrachovec,; and Edward J. Novotny. Clinical Standard Work in the Treatment of Pediatric Status Epilepticus AES 2018

Invited Lectures:

1. Genetic Control of Mitochondrial Function in Human Disease -- Presented at the Child Neurology Society Meeting in Memphis, TN on October 11, 1985.
2. Normal Development of the Human Electroencephalogram -- Presented at the annual meeting of the Western Society of EEG Technologists on November 7, 1985.
3. NIMH, Investigation of Cerebral Metabolism with NMR Spectroscopy. Oct, 1991
4. Society of Pediatric Research /American Pediatric Society -- Featured Speaker Presentation Metabolism and Diabetes May, 4, 1992.
5. Houston Epilepsy Association - Functional Imaging in the Evaluation of Epilepsy - May 16, 1992.
2. Boston Children's Hospital - Cerebral amino acid turnover studied by NMR spectroscopy March 1993.
3. Montreal Neurological Institute - Killiam Lecture - 12/14/93
4. Montreal Children's Hospital – Applications of Multinuclear magnetic resonance spectroscopy to investigations of cerebral metabolism – 12/14/93
5. American EEG Society Annual Meeting - Moderator - Quest for the Source: Multidisciplinary Approaches to Functional Imaging - Chicago, IL 9/20/94.
6. International Society for Neurochemistry - Kyoto, Japan - 7/7/95
7. International Symposium on Neonatal Hypoglycemia - Kobe, Japan - 11/18/95.
8. Will Foundation Conference on Glucose Transporter Deficiency - 11/8-9/96.
9. United Leukodystrophy Foundation - Scientific Session - 7/11/97.
10. ADA Symposium on Hypoglycemia - Albuquerque, NM - 9/21/97.
11. International Symposium on Hypoglycemia in Infancy and Childhood - London, England 11/14/97.
12. Child Neurology Society – Symposium on Non-invasive Neuroimaging - Montreal, Canada 10/23/98.
13. Symposium on Genetic Insights in Paediatric Endocrinology & Metabolism – Cambridge, England. 12/13-15/1998.
14. American Epilepsy Society – Brain Imaging Techniques in Children with Epilepsy – Orlando, FL. 12/3/99.
15. NIH workshop NINDS - NIRS as a Cerebral Function Monitor in the neonate. Washington, DC. 5/5/1999.
16. NIH workshop NIAAA Ketone bodies as therapy for brain disorders Washington, DC. 5/5/2000.
17. International Conference on Developmental Cerebral Blood Flow and Metabolism, Hershey, PA. 6/8 –6/11/2000.
18. NIH workshop NIDDK/JDF – Hypoglycemia and the Brain. Washington, DC. 9/7/2000. http://www.jdrf.org/research/workshop090800.pdf.
19. Second International Conference on Neuroimaging in Epilepsy, Birmingham, AL. 10/2000.
20. 17th International Diabetes Federation Congress – Mexico City, Mexico 11/5 –10/2000.
21. THIRTY-FOURTH ANNUAL WINTER CONFERENCE ON BRAIN RESEARCH, Steamboat Springs, CO. January 20-27, 2001

22. Ketogenic diet Workshop – Pediatric Epilepsy Research Center Seattle WA Feb 2001
23. New England Regional Genetics Group, November 27, 2001, New Hampshire. Neurological manifestation of Mitochondrial Disorders
24. 3rd Annual Rett Syndrome Symposium, Baltimore MD June 17-19, 2002. Magnetic Resonance Spectroscopy of neurotransmitters in the developing nervous system.
25. Pediatric Epilepsy Advances- Cleveland Clinic Foundation, "MRS in Pediatric Epilepsy", May 2002, Cleveland, OH.
26. Developmental Brain Metabolism by C13 MRS - C13 NMR Society of Japan – Tokyo University, Tokyo, Japan 11/15/2002
27. MRS in Pediatric Neurological Disorders – National Center of Neurology and Psychiatry, Tokyo, Japan, 11/17/2002
28. Advances in Pediatric Epileptology – Dokkyo University, Tochigi, Japan, 11/19/2002
29. MRS in Pediatric Neurological Disorders – Japanese Child Neurology Society Osaka, Japan, 11/21/2002
30. Neuroimaging Insights on Normal Development and Neurologic Disease: Principles and Applications "MR Spectroscopy" - **Symposium IV 31st Annual Meeting of the Child Neurology Society** – Washington DC, 10/10/2002
31. Developmental Neuroimaging – Neurology Grand Rounds - Children's Hospital of Boston/Longwood Neurology – Boston, MA, 12/11/2002
32. Developmental Neuroimaging – Neurology Grand Rounds – UTSW Medical Center Dallas, TX – 4/9/2003
33. Developmental Neuroimaging – Pediatric Grand Rounds - Mt. Sinai – New York, NY 11/2003
34. Developmental Neuroimaging – Dartmouth Hitchcock Neurology Grand rounds 4/9/2004
35. Unfocusing in on Epilepsy – Dartmouth Hitchcock Neurology Grand rounds 5/2005
36. Translating Autism Spectrum Disorders: Bench to Bedside and Beyond – "Childhood Epilepsy in Autistic Spectrum Disorders"; Fairfield University, 6/12/2006
37. Epilepsy Surgery in Childhood – Mitra Hospital, Athens, Greece - 11/18/2006
38. Pediatric Grand Rounds -Cornell –Weill School of medicine - *"Epilepsy Surgery in Childhood"*- New York, NY- November 21, 2006
39. Neurology and Neuroscience Grand Rounds - Weill – Cornell School of Medicine New York, NY - "Shifting the Focus on Epilepsy" - November 22, 2006
40. Epilepsy and Clinical Neurophysiology Rounds – Massachusetts General Hospital, Boston, MA November 30th, 2007.
41. Neuroimaging in Pediatric Epilepsy – University of California San Diego, Pediatric Grand Rounds. February 29th, 2008.
42. Epilepsy Syndromes– University of Washington, Neurology Grand Rounds, 08/04/2011.
43. Molecular Diagnostic Studies of Epilepsy: Impact on Clinical Management – University of Washington, Neurology Grand Rounds, 1/10/2013.
44. 6th International Epilepsy Colloquim- Corticography in Pediatric Tumors –How can it Help?. Cleveland Clinic, 5/23/2013.
45. **Neuroscience Grand Rounds, University of British Columbia, Neurology, "**Six Degrees of Separation in Epilepsy", October 9, 2013.
46. **British Columbia Epilepsy Symposium.** Neuroimaging in Epilepsy, November 1,

2014. Vancouver, British Columbia.

47. **International Society for Magnetic Resonance in Medicine,** 23rd Annual Meeting. NEURO 2 – Educational course. "Pediatric Epilepsy: What the Clinician Wants". May 31, 2015. Toronto, Canada.
48. **Peking University International Pediatric Epilepsy Forum 2016**. "Neuroimaging in Pediatric Epilepsy". April 2- 3, 2016
49. Pediatric Grand Rounds, Seattle Children's Hospital/ UW Dept of Pediatrics. "Pediatric Epilepsy: Five New Things" August 24, 2017. Seattle, WA.
50. University of California, San Diego Neurosciences Grand Rounds. "A Mosaic of Genes, Neuroimaging and Epilepsy Surgery" September 29, 2017. La Jolla, CA.
51. Florida Hospital for Children, Pediatric Grand Rounds. "Pediatric Epilepsy Neuroimaging". October 18, 2017. Orlando, FL
52. Behavioral Aspects of Neurological Disorders – 2018; "Pediatric Aspects of Mood Disorders and NES", February 8, 2018 Sun Valley Resort, Sun Valley, Idaho

TRAINEES
Undergraduate -
Claire Knodell - Yale 2009 Scholars of Technology and Research (STARS) program, "Neuroimaging Advancements in the Field of Epilepsy for Surgical Candidates with Partial or Focal Epilepsy"

Medical Student – Thesis Advisor

Ref Type : Thesis/Dissertation
Ref ID : 3414
Title : Processing strategies for functional magnetic resonance imaging of the visual system in occipital lobe epilepsy
Authors : ***Epstein, Richard William***;
Pub Date : 1996
Notes : by Richard William Epstein.

Thesis (M.D.) - Yale University, 1996.

FELLOWS:

<u>Clinical Neurophysiology/Epilepsy Fellows as Director of Pediatric Epilepsy at Yale</u>

Hal Blumenfeld MD, PhD Columbia University 1997-1999
Postdoctoral Fellow, Epilepsy

Cerebral blood flow imaging in subcortical brain regions with seizures
Assistant Professor, Neurology and Neurobiology – Yale University

Christopher Bradley M.D., Ph.D. 2002-2004
Postdoctoral Fellow, Epilepsy

Private Practice, Neurology, PA

Michael Chen MD 2003-2004
Postdoctoral Fellow, Clinical Neurophysiology

Clinical neurophysiology of peripheral nerve disorders
Assistant Professor, Neurology Rush Medical Center

Kamil Detniecki, MD University of Warsaw 2007-2009
Postdoctoral Fellow, Epilepsy

Instructor in Neurology, Yale University

Evan Fertig MD UMDNJ-New Jersey Med Sch 2003-2005
Postdoctoral Fellow, Epilepsy
Genetics of localization-related epilepsies
Private Practice, Northeast Regional Epilepsy Group

Jonathan Goldstein MD Brown University 1992-1994
Postdoctoral Fellow, Clinical Neurophysiology
Clinical neurophysiology of peripheral nerve disorders
Associate Professor, Neurology - Yale University, Director Clinical Neurophysiology Laboratory

Hamada Hamid DO, MPH Michigan State University 2006-2008
Postdoctoral Fellow, Epilepsy
Diffusion Tensor Imaging in temporal lobe epilepsy
Assistant Professor, Neurology – Yale University

Anjum Hashim MD UMDNJ Med School 2005-2006
Postdoctoral Fellow, Epilepsy
Assistant Professor Neurology, UMDNJ

Heidi Henninger MD University of California, San Francisco 1998-2000
Postdoctoral Fellow, Epilepsy
Mechanisms of cerebral GABA abnormalities in human epilepsy
Neurology Practice, Portland ME

Stephen Holloway MD Northwestern University 1994-1996
Postdoctoral Fellow, Clinical Neurophysiology
Localization of slow wave potentials in human neurological disorders
Assistant Professor, Neurology – University of Minnesota

Omotola Hope MD Univ of Pennsylvania Sch of Med 2003-2004
Postdoctoral Fellow, Epilepsy
Assistant Professor Neurology, Univ of Texas, Houston

Linda Huh MD University of Toronto 2005-2007
Postdoctoral Fellow, Epilepsy
Assistant Professor Neurology and Pediatrics, BC Children's Hospital Vancouver, BC

Ami Katz MD Tel Aviv University 1990-1992
Postdoctoral Fellow, Epilepsy
Neuroimaging in temporal lobe epilepsy
Private Practice, Neurology, CT

Howard L. Kim MD Northwestern University School of Medicine 1990-1992
Postdoctoral Fellow, Epilepsy
Associate Clinical Professor, University of California, Irvine

Ewa Koziorynska MD Pomorska Akad Med 2002-2004
Postdoctoral Fellow, Epilepsy
Assistant Professor, Neurology – SUNY

David Marks MD University of Cape Town 1989 – 1991
Postdoctoral Fellow, Epilepsy
Clinical neurophysiology and functional imaging in extratemporal epilepsy
Assistant Professor of Neurology, UMDNJ

Lorianne Masuoka MD University of California, Davis 1993- 1995
Postdoctoral Fellow, Epilepsy
Functional neuroimaging in occipital lobe epilepsy
Assistant Director of Clinical Neuroscience Research, Berlex Laboratories

Stephen Novella MD Georgetown University 1995-1996
Postdoctoral Fellow, Clinical Neurophysiology
Clinical neurophysiological evaluation of Diabetes
Assistant Professor, Neurology – Yale University

Dang Nguyen MD Montreal University 1999-2001
Postdoctoral Fellow, Epilepsy
Levetiracetam in adult and pediatric epilepsy
Hypothalamic hamartomas
Assistant Professor of Neurology, Montreal

Steve Pacia MD Medical College of Wisc 1991-1992
Postdoctoral Fellow, Epilepsy
Clinical Neurophysiology of temporal lobe epilepsy
Assistant Professor of Neurology, NYU

Jose Padin-Rosado MD Universidad Central del Caribe School of Medicine 2007-2009
Postdoctoral Fellow, Epilepsy
Clinical Neurophysiology of extratemporal epilepsy
Assistant Professor of Neurology, University of New Mexico

A. Lebron Paige MD University of Miami School of Medicine 2002-2004
Postdoctoral Fellow, Epilepsy
Cerebral blood flow imaging in epilepsy by SPECT
Associate Professor, Neurology - University of Iowa

Susanne Patrick-Mackinnon MD 1994-1995
Postdoctoral Fellow, Clinical Neurophysiology

Huned Patwa MD New York University 1996-1997
Postdoctoral Fellow, Clinical Neurophysiology
Clinical neurophysiology of neuromuscular diseases
Assistant Professor, Neurology – Yale University

Christopher Ransom MD, PhD University of Alabama 2007-2010
Postdoctoral Fellow, Epilepsy
Assistant Professor, Neurology – University of Washington

Gautami Rao MD 2004-2006
Postdoctoral Fellow, Epilepsy
Private Practice, Westchester, NY

Sanjay P. Singh MD Georgetown University 1999-2001
Postdoctoral Fellow, Epilepsy
Professor of Neurology, Chairman, Creighton University

David Tinklepaugh M.D. 2002-2003
Postdoctoral Fellow, Clinical Neurophysiology
Clinical neurophysiology of peripheral nerve disorders
Private Practice Neurology, Norwich, CT

David Tkeshelashvili MD Tbilisi State Medical School 1999-2000
Postdoctoral Fellow, Epilepsy
Intraoperative monitoring in human epilepsy
1998-1999
Postdoctoral Fellow, Clinical Neurophysiology
Dipole localization of the human epileptic focus
Private practice, Waterbury, CT

James Thompson, MD Medical College of Georgia 1997-1999
Postdoctoral Fellow, Epilepsy
Dipole localization of the human temporal lobe focus
Neurology Practice, Norwalk, CT

Hajime Tokuno, MD George Washington University 1997-1998
Postdoctoral Fellow, Clinical Neurophysiology
Neuroimaging in stroke
Associate research scientist, Neurology – Yale University

Megdad Zaatreh, MD 1999-2001
Postdoctoral Fellow, Epilepsy
Frontal Lobe epilepsy
Private Practice, Northeast Regional Epilepsy Group

Director of Epilepsy Program, Seattle Children's Hospital, University of Washington

Carter Wray, MD 2009-2011
Postdoctoral Fellow, Epilepsy
Assistant Professor, Oregon Health Sciences Univ.

Sharon McDaniel, MD Washington University School of Medicine, St. Louis, Missouri. 2010 - 2012
Postdoctoral Fellow, Clinical Neurophysiology and Epilepsy
Head Pediatric Epilepsy, Kaiser Foundation Redwood City, CA

Elizabeth Simard-Tremblay, MD University of Sherbrooke, Sherbrooke, Quebec, Canada 2011-2013
Postdoctoral Fellow, Clinical Neurophysiology and Epilepsy
Pediatric Epilepsy, Montreal Children's Hospital

Seema Afridi, MD Southern Illinois University – School of Medicine 2012-2013
Postdoctoral Fellow, Clinical Neurophysiology
Private Practice, Bellingham, WA

Juan Piantino, MD University of Buenos Aires, School of Medicine 2013-2014
Postdoctoral Fellow, Epilepsy
Pediatric Neurology, OHSU, Portland, OR

Chris Beatty, MD Case Western Reserve University 2014-2016
Postdoctoral Fellow, Clinical Neurophysiology and Epilepsy
Pediatric Epilepsy, Charlotte, North Carolina

Stephanie (Carapetian) Randle, MD Rosalind Franklin University 2015-2016
Postdoctoral Fellow, Clinical Neurophysiology
Pediatric Neurology, Seattle Children's Hospital/University of Washington

Jason Lockrow, MD, PhD Medical University of South Carolina 2016-2018
Postdoctoral Fellow, Clinical Neurophysiology and Epilepsy
Pediatric Neurology, Seattle Children's Hospital/University of Washington

Washington State Health Care Authority

Vagal nerve stimulation for epilepsy and depression

Emily Transue, MD, MHA
Associate Medical Director
Health Care Authority
Friday, May 15, 2020

Washington State Health Care Authority

Background

- The vagal nerve (10th cranial nerve) is the longest autonomic nerve and interfaces with parasympathetic control of the heart, lungs, and GI tract
- Vagal nerve stimulation (VNS) has been studied for treatment of epilepsy and depression; it has also been considered for treatment of fibromyalgia and migraines
- The nerve can be stimulated via a transmitter implanted below the clavicle and electrodes wrapped around the left vagal nerve at the carotid sheath
- Transcutaneous stimulation at the ear (tVNS) has also been studied
- Mechanism of action of VNS is poorly understood but is presumed to involve neuromodulatory effects

2

HTCC VNS History

- VNS for epilepsy and depression was evaluated by the Washington Health Technology Clinical Committee in 2009
  - Covered for management of epileptic seizures in patients twelve years of age or older that have a medically refractory seizure disorder
  - Non-covered for management of depression
- Updated literature search in 2013 did not show new evidence indicating a need for re-review
- In 2017, the FDA lowered the age for coverage of VNS for epilepsy from 12 to 4
- The 2009 HTCC review did not address children under 12; need for a policy around children age 4-12 led to requests for a re-review by HTCC

3

Policy question

- Should Vagal Nerve Stimulation (VNS) be covered for epilepsy, and if so, under which conditions?
  - Included in this question: Should the existing age limitations from the 2009 HTCC decision be maintained or removed?
- Should Vagal Nerve Stimulation (VNS) be covered for depression, and if so, under which conditions?
- Should transcutaneous Vagal Nerve Stimulation (tVNS) be covered, and if so, under which conditions?

4

Washington State Health Care Authority

Current State Agency Policy on VNS

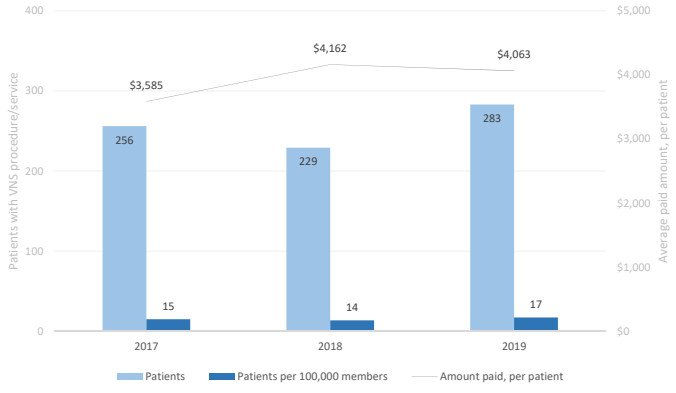
	Epilepsy for patients 12 and older	Depression
PEBB/SEBB/UMP	Covered for refractory epilepsy (per HTCC)	Non Covered (per HTCC)
MEDICAID	Covered for refractory epilepsy (per HTCC)	Non Covered (per HTCC)
LABOR AND INDUSTRIES	Covered for refractory epilepsy (per HTCC)	Non Covered (per HTCC)

5

Washington State Health Care Authority

Current Utilization

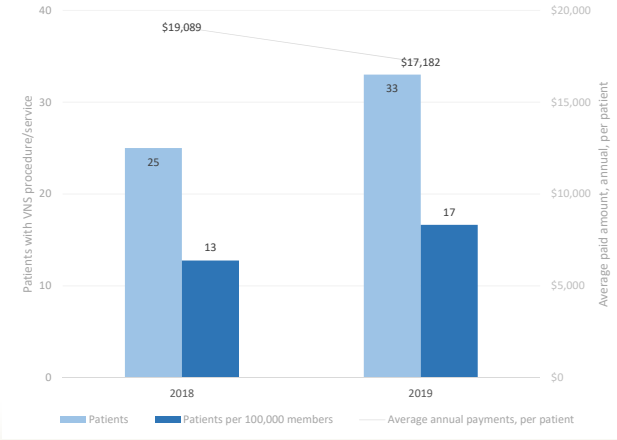
Medicaid (FFS/MC), 2017-2019: All VNS procedures



6

Current Utilization

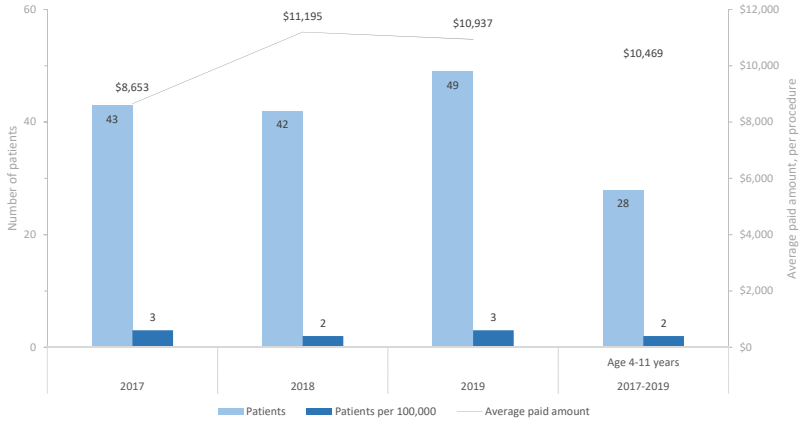
PEBB/UMP, 2018-2019: All VNS Procedures



7

Current Utilization

VNS implantation procedures, SFY 2017-2019
Medicaid (FFS/MC)



8

Costs: Implementation and subsequent years

Table. 3-year encounters and paid amounts, all VNS procedures among members that received a VNS implant in SFY 2017

Medicaid (FFS and MC)				
Year (SFY)	Patients	Encounters	Paid amount	Avg. paid amount, per patient
2017	43	230	$418,384	$9,730
2018	26	72	$10,910	$420
2019	18	38	$3,288	$183

Data note: Paid amount includes all professional and ancillary fees associated with the VNS-related procedure code.

9

Coverage comparisons

- Medicare: National Coverage Decision
  - VNS is **reasonable and necessary** for patients with **medically refractory partial onset** seizures for whom **surgery is not recommended** or for whom surgery has **failed**
  - VNS is not reasonable and necessary for all other types of seizure disorders which are medically refractory and for whom surgery is not recommended or for whom surgery has failed
  - Depression: Covered only in the setting of a clinical trial
- No Local Coverage Decision

10

Coverage comparisons: Aetna

- VNS medically necessary for:
  - Members with **focal seizures** who remain **refractory to optimal antiepileptic medications and/or surgical intervention**, or who have **debilitating side effects** from antiepileptic medications, and who have no history of a bilateral or left cervical vagotomy
  - Members with **Lennox-Gastaut** syndrome who remain refractory to optimal antiepileptic medications, and/or surgical intervention, or who have debilitating side effects from antiepileptic medications, and who have no history of a bilateral or left cervical vagotomy
- tVNS experimental/investigational for epilepsy
- VNS and tVNS experimental/investigational for depression

11

Coverage comparisons: Regence

- VNS is medically necessary for members with **medically refractory seizures** who have tried and been unresponsive to, or intolerant of, at least **2 anti-epileptic drugs** (AEDs).
- Regence considers the use of VNS for all other indications including depression, and the use of tVNS, as investigational

12

Coverage comparisons: Cigna

- VNS is medically necessary for the treatment of **medically intractable seizures** when there is **failure, contraindication or intolerance** to all suitable **medical and pharmacological** management
- VNS is experimental, investigational, or unproven for any other indication including, but not limited to, refractory depression
- tVNS is experimental, investigational, or unproven for any indication

13

Guidelines: VNS for Epilepsy

National Institute for Health and Care Excellence (NICE), 2012

VNS is indicated for adults, children and young people with epilepsy who are **refractory to medication but unsuitable for surgery**. This applies to those with **focal or generalized** seizures. (Good quality.)

Scottish Intercollegiate Guidelines Network (SIGN), 2015

Vagus nerve stimulation may be considered in adult patients with epilepsy who are **medically refractory** and who have been found to be **unsuitable for resective surgery**. (Good quality.)

Task Force Report for the Int'l League Against Epilepsy Commission of Pediatrics, 2015: Infantile Epilepsy

Infants with medically refractory seizures who are not suitable candidates for epilepsy surgery **may be considered** for VNS (expert opinion and standard practice; optimal level care at tertiary/quaternary facilities) (Fair quality.)

14

Guidelines: VNS for Depression

Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, 2014 (Spain)

The use of VNS outside the scope of research is **discouraged** due to the invasive nature of the procedure, uncertainty about its efficacy and adverse effects. (Good quality)

Canadian Network for Mood and Anxiety Treatments, 2016

VNS recommended as **third-line treatment**, after first-line treatment of repetitive transcranial magnetic stimulation and electroconvulsive therapy as second-line treatment for adults with major depressive disorder. (Fair quality)

Department of Veterans Affairs, Dep't of Defense, 2016

We **recommend against** offering VNS for patients with major depressive disorder, including patients with severe treatment-resistant depression, outside of a research setting. (Fair quality)

15

Agency Medical Director Concerns

Safety = High

Efficacy = High

Cost = High

16

Key Questions: Epilepsy

1. What is the evidence on the efficacy and effectiveness of VNS1 in adults and children with epilepsy?
2. What direct harms are associated with VNS in adults and children with epilepsy?
3. Do important efficacy/effectiveness outcomes or direct harms of VNS in adults and children with epilepsy vary by:
   - a. Patient characteristics (e.g., age, time since diagnosis)
   - b. Type of seizure
   - c. Duration of treatment
   - d. Intensity of treatment
4. What are the cost-effectiveness and other economic outcomes of VNS in adults and children with epilepsy?

17

Key Questions: Depression

1. What is the evidence on the efficacy and effectiveness of VNS in adults with TRD?
2. What direct harms are associated with VNS in adults with TRD?
3. Do important efficacy/effectiveness outcomes or direct harms of VNS in adults with TRD vary by:
   - a. Patient characteristics (e.g., age)
   - b. Duration or type of depression (e.g., unipolar vs. bipolar)
   - c. Duration of treatment
   - d. Intensity of treatment
4. What are the cost-effectiveness and other economic outcomes of VNS in adults with TRD?

18

Washington State Health Care Authority

Epilepsy evidence

RCTs:

Study	Comparator	Age	Seizure type
Bauer et al	High vs low stim tVNS	18 to 35	Any type
Handforth, Dodrill	High vs low stim VNS	12 to 65	Partial onset (w or w/o generalization)
Klinkenberg	High vs low stim VNS	4 to 18	Any type
Landy	High vs low stim VNS	Adult	Focal/Complex partial seizures
Ryvlin	VNS/BMP vs BMP	16-75	Focal
Elger	High vs low stim VNS	12 and older	Predominantly focal seizures

15 Non-Randomized Trials (NRTs)

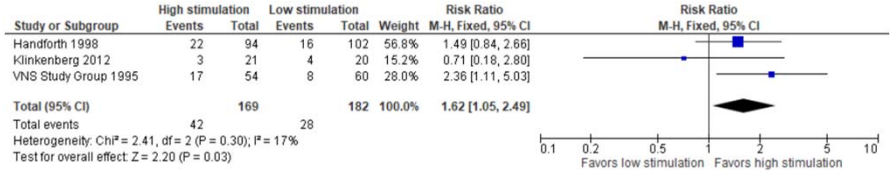
Nearly all trials identified had moderate to high risk of bias and low degree of confidence

19

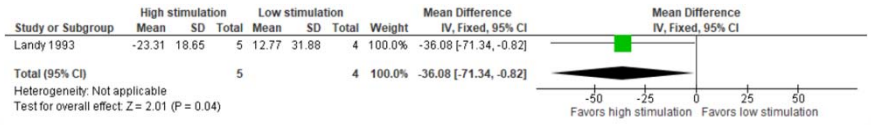
Washington State Health Care Authority

Epilepsy: Benefits
High stim VNS vs low stim (sham) VNS

Rate of Response: 50% or greater reduction in seizure frequency



Reduction in Seizure Frequency



20

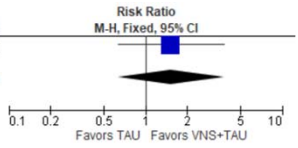
Washington State Health Care Authority

Epilepsy: Benefits
VNS vs. treatment as usual (TAU)

Rate of Response: defined as 50% or greater reduction in seizure frequency

Study or Subgroup	VNS+TAU Events	VNS+TAU Total	TAU Events	TAU Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rylin 2014	10	54	7	58	100.0%	1.53 [0.63, 3.74]
Total (95% CI)		54		58	100.0%	1.53 [0.63, 3.74]
Total events	10		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)



21

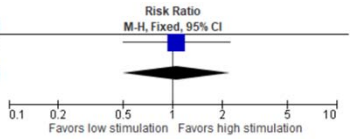
Washington State Health Care Authority

Epilepsy: Benefits
tVNS

Rate of Response: defined as 50% or greater reduction in seizure frequency

Study or Subgroup	High stimulation Events	High stimulation Total	Low stimulation Events	Low stimulation Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bauer 2016	10	37	10	39	100.0%	1.05 [0.50, 2.24]
Total (95% CI)		37		39	100.0%	1.05 [0.50, 2.24]
Total events	10		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.14 (P = 0.89)



22

Epilepsy: Harms

	Treatment withdrawal	Hoarseness	Cough	Dyspnea	Pain	Paresthesia	Nausea	Headache
Comparator								
VNS high vs VNS low	2.5 (0.5–12.7)	2.32 (1.6–3.4)	1.04 (0.7–1.6)	2.45 (1.1–5.6)	1.01 (0.6–1.7)	0.78 (0.39–1.5)	0.72 (0.32–1.62)	0.9 (0.48–1.7)
VNS vs TAU	0.84 (0.5–1.2)	18.24 (0.44–750)	7.51 (0.16–358)	7.51 (0.16–358)	7.51 (0.16–358)	7.51 (0.16–358)		7.51 (0.16–358)
tVNS high vs low	1.32 (0.58–2.97)				2.11 (0.38–11.8)		1.05 (0.14–7.93)	0.9 (0.4–2.06)

23

Epilepsy: Additional policy question

- Definitions of “medically refractory” vary between different studies and guidelines
- Adequate therapeutic trial of 2-4 drugs typical
- Likelihood of response diminishes with each add’l drug
- International League Against Epilepsy (ILAE) task force: “failure of adequate trials of two tolerated, appropriately chosen and administered antiseizure drugs (monotherapy or combination) to achieve seizure freedom”
- However, a follow up study* noted that particularly in children, 23-25% of those classified as intractable by this ILAE standard would achieve sustained response with additional medication; suggested threshold of 3 rather than 2 med trials

*Ramos-Lizana et al, Seizure 21(4), May 2012.

24

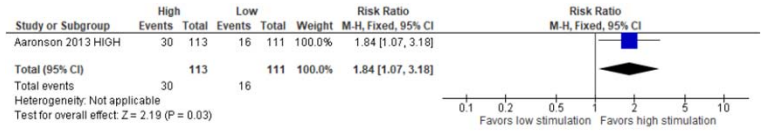
Depression: Evidence

- 5 studies evaluating risks and harms, published in 9 publications
  - 2 RCTs with moderate risk of bias
  - 1 NRS with moderate risk of bias
  - 2 NRS with high risk of bias

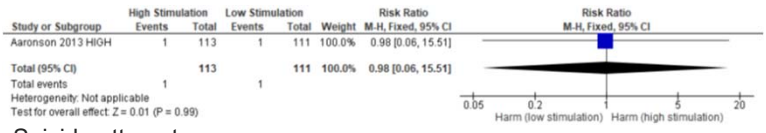
25

Depression: Benefits
High- vs Low-stimulation

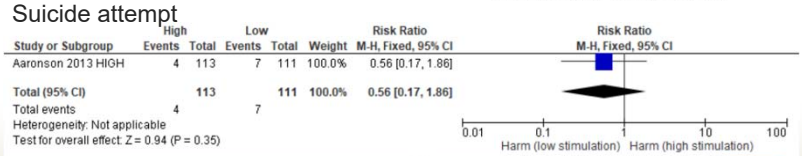
50% reduction in MADRS depression score



Suicide death



Suicide attempt

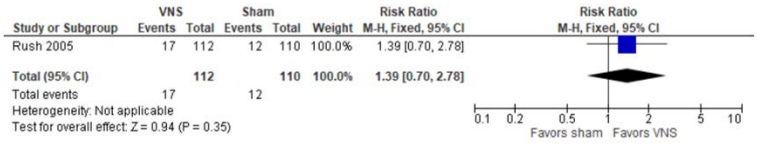


26

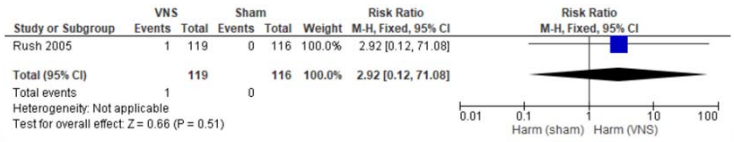
Washington State Health Care Authority

Depression: Benefits
VNS vs Sham

50% reduction in MADRS depression score



Suicide death



27

Washington State Health Care Authority

Depression: Harms

	Treatment withdrawal	Hoarseness	Cough	Dyspnea	Pain	Paresthesia	Nausea	Headache
Comparator								
VNS high vs VNS low	0.39 (0.08–1.98)	1.19 (0.95–1.49)	1.02 (0.56–1.86)	1.13 (0.68–1.88)	1.65 (0.99–2.74)	1.24 (0.74–2.07)	0.59 (0.21–1.65)	1.09 (0.52–2.27)
VNS vs sham VNS	6.88 (0.36–131)	1.79 (1.27–2.54)	3.10 (1.36–7.07)	1.64 (0.78–3.45)	2.03 (0.88–4.70)	1.54 (0.63–3.75)	2.11 (0.62–7.20)	
VNS vs TAU	Not reported							
tVNS high vs low	Not reported							

28

Risks: Other

- FDA MAUDE (Manufacturer and User Facility Device Experience database) review
  - Multiple reports of bradycardia, some with asystole up to 15 seconds and some resulting in “drop” episodes
  - Most patients had normal baseline EKG
  - Reported episodes resolved with turning off or removing the VNS device
  - This complication is believed to be rare but potentially very serious

29

Differential impact by patient characteristics

- No major distinctions by patient subgroups for either depression or epilepsy

30

Cost effectiveness

- VNS for epilepsy: very limited data
  - In children with **tuberous sclerosis** who had failed 2 meds, VNS had a 5 year cost of $50,742 for 3.89 QALYs **($13K/QALY);** under willingness to pay threshold but less cost effective than additional meds or ketogenic diet (Fallah et al)
  - Estimate for children age 12 and older with drug-resistant partial-onset seizures: **5 year net cost savings of $77,480** per patient (21.5% of costs) relative to medication alone. Seizure related hospitalization was the main cost driver. VNS placement costs offset 1.7 years after placement.

31

Cost effectiveness

- VNS for depression:
  - No data
- tVNS for depression or epilepsy:
  - No data

32

Agency Medical Director Group
Recommendation: Vagal Nerve Stimulation for Epilepsy

- Covered with conditions
- VNS for epilepsy is medically necessary when all of the following are met:
  - Seizure disorder is refractory to medical treatment, defined as at least 3 adequate trials of anti-epileptic medication
  - Surgical treatment is not recommended or has failed

33

Agency Medical Director Group
Recommendation: Vagal Nerve Stimulation for Depression

- Vagal Nerve Stimulation for Depression is not covered
- Rationale:
  - Compelling evidence for the effectiveness and safety of this approach is lacking
  - Multiple other effective modalities for management of treatment resistant depression exist and are covered
  - Re-review may be indicated once the results of the large clinical trial finishing in 2022 become available

34

Agency Medical Director Group
Recommendation: Transcutaneous Vagal Nerve Stimulation

- tVNS is not covered

35

Questions?

More Information:
HTA topic webpage

Emily Transue, MD, MHA
Associate Medical Director
Health Care Authority
shtap@hca.wa.gov
Tel: 360-725-5126

36

Washington State Health Care Authority

Order of scheduled presentations:

Vagal nerve stimulation for epilepsy and depression

	Name	
1	Gwinn Ryder, MD, Cathy Hill	Center for Neurologic Restoration, Swedish Neuroscience Institute American Association of Neurological Surgeons/ Congress of Neurological Surgeons, American Society for Stereotactic and Functional Neurosurgery Washington State Association of Neurological Surgeons
2	Rebecca M. Allen, MD, MPH Joshua Bess, MD	Washington State Psychiatric Association
3	David L. Dunner, MD	Director, Center for Anxiety and Depression
4	Lorenzo Dicarlo, MD Scott Aaronson, MD Charles Conway, MD	LivaNova

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: _____

_____

_____

_____

*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.

[redacted] 4/23/20 Ryder Gwinn, MD

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: ryder.gwinn@swedish.org

Phone Number: 206-852-4052

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:

	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 employed by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons Washington Office as the Senior Manager for Regulatory Affairs. I do not receive any compensation from any manufacturers.

*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.

[redacted]

X _____ **Catherine J. Hill**

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: chill@neurosurgery.org

Phone Number: 202-446-2026

Washington State Healthcare Authority
Health Technology Assessment Program

Re-review of Vagus Nerve Stimulation (VNS) for Epilepsy and Depression

Ryder Gwinn, MD
Interim Executive Medical Director, Swedish Neuroscience Institute
Medical Director, Center for Neurologic Restoration
Swedish Neuroscience Institute
550 17th Ave. Suite 540
Seattle, WA 98122

Washington State Health Care Authority

Vagal Nerve Stimulation for Epilepsy and Depression: Final Evidence Report

Depression

We found 5 studies, reported in 9 publications, which evaluated the benefits and harms of VNS for depression.

- High- vs. Low-Stimulation VNS
  - High-stimulation **VNS had higher rates of response, defined as 50% MADRS reduction**, compared with low-stimulation VNS (low-quality evidence, based on 1 RCT), but was not associated with reduced depression severity (low-quality evidence, based on 1 RCT) or lower rates of suicide or attempted suicide (very-low-quality evidence, based on 1 RCT).
  - High-stimulation and low-stimulation VNS had similar number of withdrawals, rates of voice alteration or hoarseness, cough, dyspnea, pain, nausea, and headache (very-low- to low- quality evidence, based on 1 RCT).
- VNS vs. Sham VNS
  - Compared with sham VNS, VNS was not associated with reduced depression severity (moderate-quality evidence, based on 1 RCT), or with lower rates of suicides (very-low- quality evidence, based on 1 RCT). VNS and sham VNS also had similar rates of response, defined as 50% MADRS reduction (very-low-quality evidence, based on 1 RCT).
  - VNS, when compared with sham VNS, has higher levels of voice alteration or hoarseness and cough (moderate-quality evidence, based on 1 RCT), but similar number of withdrawals, dyspnea, pain, paresthesias, and nausea (very-low- to low-quality evidence, based on 1 RCT).
- VNS vs. Treatment as Usual
  - **VNS with TAU was more effective in reducing depression symptoms and had higher response rates than TAU alone** (very-low-quality evidence, based on 1 NRS), but may be associated with higher rates of attempted suicide or self-inflicted injury, but the evidence is very uncertain and may reflect greater severity of depression (very-low-quality evidence, based on 1 NRS). **VNS may be associated with lower mortality rates**, but study results are not consistent (very-low-quality evidence, based on 2 NRS).
  - VNS has lower withdrawal rates than TAU (very-low-quality evidence, based on 1 NRS).

Summary

- VNS appears to be an appropriate treatment option for adults and children with treatment- resistant epilepsy, but there is a **lack of robust evidence on the effectiveness of VNS for TRD in adults**. The use of VNS is commonly associated with minor adverse events, such as coughing and voice alteration, which are often transient and tend to decrease over time. In some cases, adverse events can be minimized through adjustment of the stimulation parameters. However, if VNS equipment or its components fail, people can be exposed to rare, but serious harms.

Depression

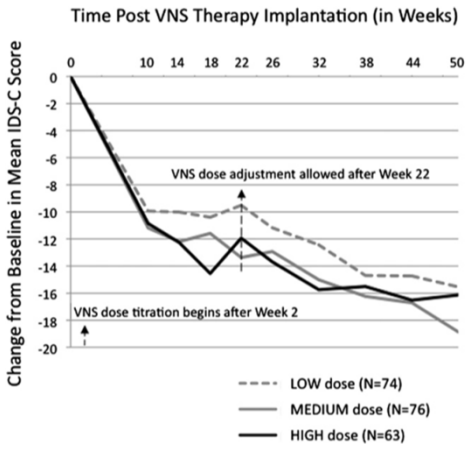
- High-stimulation VNS is associated with an ***increased response rate*** (as measured on the MADRS) when compared with low-stimulation VNS (low-quality evidence), but other outcomes, such as reduced depression severity using other scales and suicide deaths or attempts, are not different between stimulation groups (very-low to low-quality evidence).
- ***VNS with TAU reduced depressive symptoms more than TAU alone*** (very-low-quality evidence); however, the difference was small and may not be clinically meaningful.
- **VNS with TAU also resulted in higher rates of response compared with TAU alone** (very-low-quality evidence). Other outcomes were not different between groups (sham VNS or TAU) or were inconsistent, making it difficult to draw robust conclusions about the effectiveness of VNS for depression in adults. As with the use of VNS for epilepsy, patients using the VNS implant may experience voice alteration or hoarseness and coughing related to the use of VNS (very-low- to moderate -quality evidence).
- Most guidelines either recommend against the use of VNS for depression, citing a lack of evidence and calling for more research, or did not make any specific recommendations for or against the use of tVNS for depression. ***However, 1 guideline did recommend VNS as a third-line treatment, after repetitive transcranial magnetic stimulation (first-line treatment) and ECT (second-line treatment) for adults with MDD. (Canadian Network for Mood and Anxiety Treatments, 2016 – Fair quality)***
- On February 15, 2019, ***CMS issued an NCD that covers FDA-approved VNS devices for TRD through Coverage with Evidence Development***.[2] This requires patients to be entered into a CMS-approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least 1 year (Appendix H).[2] ***If trials show positive interim findings when the CMS-approved, double-blind, randomized placebo-controlled trial has completed enrollment, there is the possibility of extending the study to a prospective longitudinal study.***[2] Prior to this proposed amendment, CMS stated that VNS was not reasonable and necessary for TRD.[2] The use of VNS for other forms of depression or for use outside of a clinical trial remain noncovered.[2] At the time of writing this report, only 1 trial is approved by CMS (NCT03887715; Table 22).[102]
- There is a high level of agreement across the coverage determinations, with VNS for depression not being covered by any of the 3 commercial payers reviewed for this report.
- We identified 1 RCT that did not demonstrate any evidence of a benefit of tVNS for depression, and the guidelines and coverage policies that mentioned tVNS were not supportive of its use for depression in adults.
- We did not identify any studies reporting on economic outcomes related to the use of VNS or tVNS for depression.

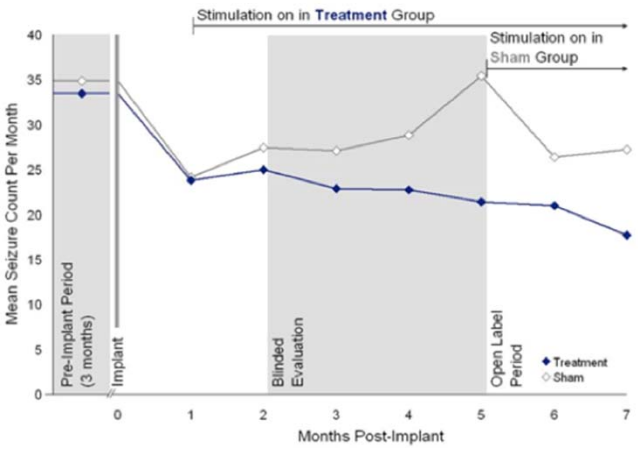
Randomized Study:

Aaronson et al., 2013: 29 academic and clinical sites in the U.S.

- Remission and Duration of Remission
  At week 22, remission (defined as score of ≤ 14 on the IDS-C and IDS-SR, ≤ 5 on the QIDS-C, or ≤ 9 on the MADRS) was not significantly different between treatment groups (reported graphically; 5% to 6% low; 9% to 11% in the medium and high groups)
- At week 50, response was numerically higher than at week 22, but there was no difference between treatment groups (reported graphically)
  - Both groups are open label at this point!

Comparison to Other Neuromodulation





RNS for Epilepsy

Comparison to Other Neuromodulation

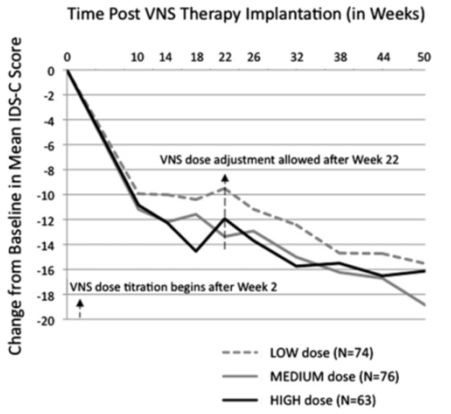
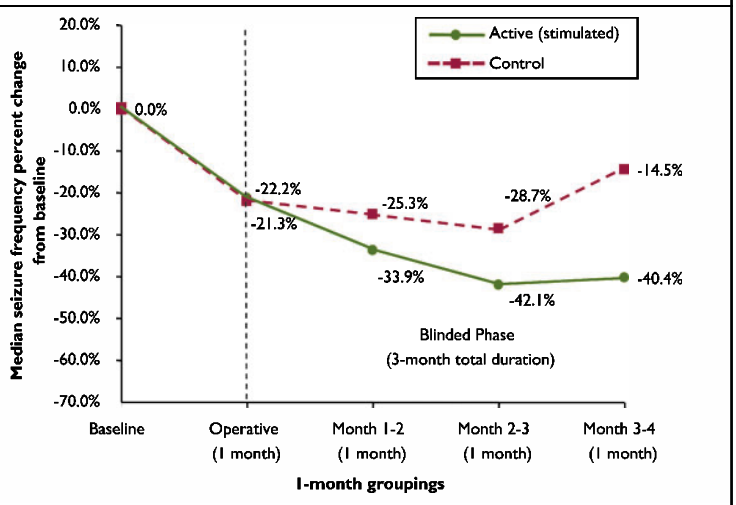
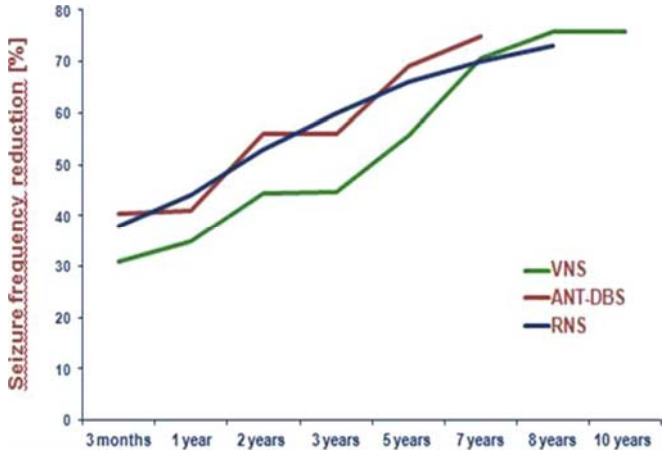


Figure 2. Per protocol analysis of change from baseline in mean IDS-C scores by treatment groups. Note that the figure presents only the patients who attained their assigned dose during the acute phase (up to Week 22).



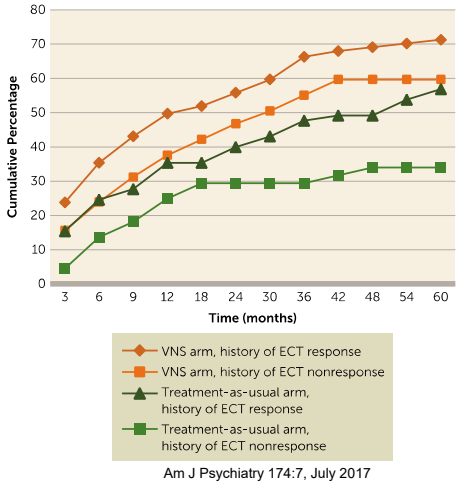
DBS for Epilepsy

Long Term Outcomes with Neuromodulation



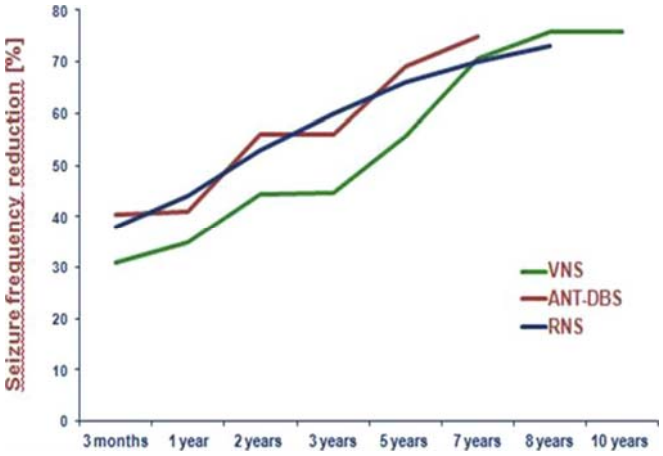
Epilepsy Research, 2019-07-01, Volume 153, Pages 71-75.

FIGURE 4. First-Time Response Among Patients With Treatment-Resistant Depression Receiving Treatment as Usual With or Without Adjunctive Vagus Nerve Stimulation (VNS): Subanalysis of Patients With a History of Response or Nonresponse to ECT[a]



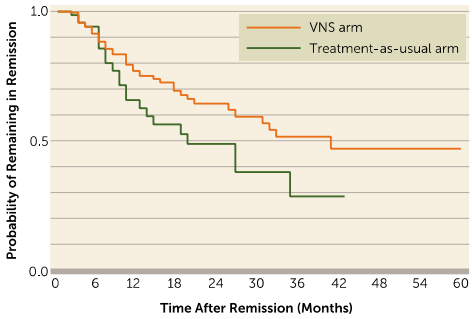
Am J Psychiatry 174:7, July 2017

Long Term Outcomes with Neuromodulation



Epilepsy Research, 2019-07-01, Volume 153, Pages 71-75.

FIGURE 3. Kaplan-Meier Plot of Time to First Recurrence After Remission Among Patients With Treatment-Resistant Depression Receiving Treatment as Usual With or Without Adjunctive Vagus Nerve Stimulation (VNS)[a]



[a] Remission was defined as a decrease to a score ≤9 on the Montgomery-Åsberg Depression Rating Scale at any postbaseline visit, and recurrence was defined as an increase to a score ≥20 for the first time after achieving remission.

Am J Psychiatry 174:7, July 2017

VNS for Depression - Summary

- Significant improvement in depression rating scores with VNS stimulation.
- Recommended as third line treatment in “fair” guidelines.
- Clear improvement in time of remission, responder rates, and mortality with VNS in 5 year open label study.
- Appears to behave like many other neuromodulation therapies with improving responder rate over time.
  - Unlikely to get complete picture with randomized/controlled trial.
- Patients with severe TRD need significantly better options.
  - Urge the WA State Healthcare Authority to cover VNS for TRD.
  - February 2019 decision memo, CMS provided a coverage pathway for patients with TRD.
    - Minimally need participatory option for WA state patients in “Coverage with Evidence” CMS trial.

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.		
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:

Board Member of the Clinical Transcranial Magnetic Stimulation Society (no direct bearing on VNS)

Partner & Director of Neuropsychiatry and Research at SeattleNTC, a clinic caring for patients with VNS

Site Principal Investigator for the RECOVER study on VNS for depression; we have only had 1 subject so far

	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: _____

Washington State Psychiatric Association, funded with annual dues by psychiatrist members

*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] 4/17/20 Rebecca M. Allen MD MPH

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: rebecca.allen@seattlentc.com

Phone Number: 206-467-6300 ext.2

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:

Study physician in a research study sponsored by LivaNova

	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: _____

*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] 4/17/2020 Joshua Bess MD

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: josh.bess@seattlentc.com

Phone Number: 206.467.6300

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:

Janssen - Speaker (2019); Rivanova - Principal Investigator for site for recover study and payment for clinical services for a former research patient; Various legal firms; Independent medical reviews, medical record reviews; depositions; civil testimony; Interpretation of reports

	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: _____

*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] 4/20/20 _____

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: [redacted]

Phone Number: [redacted]

Presentation to WA HTA re Vagus Nerve Stimulation

David L Dunner, MD, FACPscyh
Director, Center for Anxiety and Depression
Mercer Island, WA
Professor Emeritus, Department of Psychiatry and Behavioral Sciences
University of Washington

Conflicts of Interest (>$10,000)

- Janssen: Speaker 2019
- LivaNova: Principal Investigator for our site for RECOVER Study; Payment for clinical services to a former research patient (Payments less than $10,000 as of 4/20/2020)
- Various legal firms: Independent medical evaluations; review of medical records; depositions; court testimony; preparation of reports

Key Points (1)

- My background includes over 50 years of research and clinical treatment involving patients with treatment resistant major depression and bipolar depression (NIMH; Columbia University College of Physicians and Surgeons/New York State Psychiatric Institute; University of Washington, Center for Anxiety and Depression)
- My research and clinical expertise involving treatment resistant depression is recognized internationally
- Our group was the first in the Northwest to treat patients with VNS for treatment resistant depression; to treat patients with Transcranial Magnetic Stimulation; and to provide outpatient treatment with esketamine nasal spray for patient with treatment resistant depression

Key Points (2)

- Patients with severe treatment resistant depression (those who fail 4 or more antidepressant treatment trials) do not respond well to the next antidepressant treatment trial
- Patients with severe treatment resistant depression have few potentially effective treatment options (Esketamine nasal spray; Transcranial Magnetic Stimulation; Electroconvulsive Therapy; Vagus Nerve Stimulation)
- Some patients elect not to have some of the above treatment options due to potential adverse effects or other reasons (cost, convenience)

Key Points (3)

- Vagus Nerve Stimulation is an FDA approved treatment for patients with treatment resistant depression
- Vagus Nerve Stimulation is an effective treatment option for patients with treatment resistant depression, and the efficacy increases over time
- Vagus Nerve Stimulation is a safe and well tolerated treatment for patients with treatment resistant depression
- I agree that sham controlled studies prove efficacy and safety, but ignoring data from comparator studies (George et al.; Aaronson et al.) undervalues the clinical effect of Vagus Nerve Stimulation
- The Aaronson et al. study and other studies report that Vagus Nerve Stimulation reduces suicidal behavior in patients with treatment resistant depression and also reduces overall medical care costs

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.		
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:

LivaNova USA, Incorporated

	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: _____

*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] 23 April 2020 Lorenzo DiCarlo MD

Signature *Date* *Print Name*

So we may contact you regarding your presentation, please provide the following:

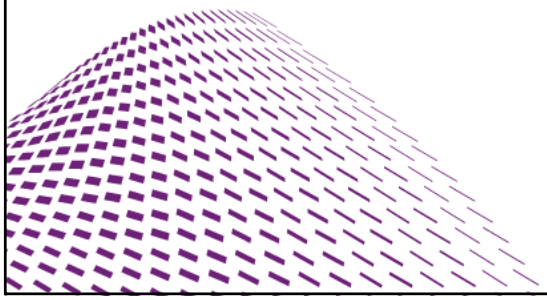
Email Address: lorenzo.dicarlo@livanova.com

Phone Number: 415 806 9000

LivaNova
Health innovation that matters

LivaNova Comments

Lorenzo DiCarlo MD
Chief Medical Officer



VNS for Treatment-Resistant Depression (TRD)

- LivaNova appreciates the WA HTA's recognition of the need for additional treatment options for patients living with depression
- Clinical data suggest that as many as 1/3 of patients continue to have debilitating symptoms even after 4 treatment interventions
- The consequence of non-responsiveness can be fatal; TRD is highly associated with suicidal ideation and suicidal attempts
- Despite this there are few treatment options available to these patients who struggle with daily living
- Those that do exist are either moderately effective, and/or associated with serious side effects such as cognitive decline
- VNS therapy was FDA approved in 2005 as adjunctive to usual and customary care for patients that have had an inadequate response to 4 or more treatment interventions

LivaNova 2

VNS for Treatment-Resistant Depression (TRD)

- Since approval, VNS therapy has been studied in the largest and longest ever post-approval study in patients whose depression was more refractory than the labeled indication
- After 5 years, in the VNS treated group:
  - 67% of patients achieved a clinical response
  - 43% of patients achieved remission, a near resolution of all symptoms
  - 50% less suicides
- It is our understanding that no other therapy in the history of treatments of depression has shown such a long-lasting treatment effect

LivaNova 3

VNS for Treatment-Resistant Depression (TRD)

- Two American Psychiatric Association (APA) documents have been published since 2007 that support the use of VNS Therapy in treating patients with TRD
- LivaNova urges WA Healthcare Authority to consider the broadest available set of evidence and the APA guidelines in order to provide patients living with TRD access to VNS as a potentially lifesaving therapy

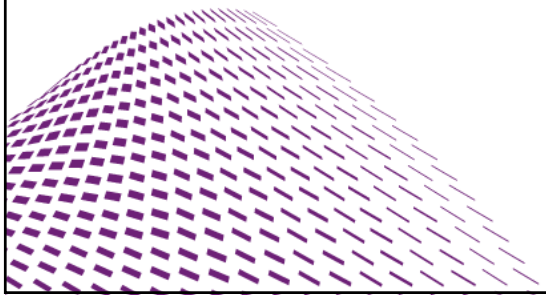
LivaNova 4

VNS for Treatment-Resistant Depression (TRD) – MEDICARE COVERAGE

- Recently CMS approved the RECOVER trial for Coverage with Evidence (CED) for new patients
- In addition, the Medicare CED provides coverage for VNS device replacement if it is required due to the end of battery life, or any other device-related malfunction
  - It is important to note that the replacement coverage is offered outside of an approved clinical trial per section D. Other in the CED
  - This is critically important for continuity of care and LivaNova requests that WA HCA will include this correction in its final report
- In addition to traditional Medicare plans, all Medicare Advantage plans must also follow this policy.

LivaNova 5

VNS for Epilepsy



LivaNova

VNS for Drug-Refractory Epilepsy (DRE)

LivaNova thanks the WSHA for conducting this HTA on Vagus Nerve Stimulation for the treatment of Drug-Resistant Epilepsy

We have several comments for your consideration

1. SUDEP publications are presented in the absence of a comparison to typical rates of SUDEP in the DRE population, and are presented in a section about VNS-related harms.

   a. We encourage the WSHA to consider the risk of SUDEP in a comparative population of epilepsy patients without VNS Therapy

   b. Ryvlin et al 2018, posits that VNS is protective against SUDEP. As such, LVN believes the relationship between VNS and SUDEP should be discussed as a benefit rather than a harm

LivaNova 7

VNS for Drug-Refractory Epilepsy (DRE)

2. The widely accepted definition of response to anti-convulsive therapy is >50% reduction in seizure frequency, and the WSHA's report conforms to this definition of "response" in the Methods section.

   a. On this basis, the retrospective and underpowered study by Jamy et al 2019 study using an unaccepted measure of success should be excluded from the HTA

LivaNova 8

VNS for Treatment-Resistant Depression (TRD) - References

Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry. 2006;163:28–40

Brådvik L, Berglund M. Long-term treatment and suicidal behavior in severe depression: ECT and antidepressant pharmacotherapy may have different effects on the occurrence and seriousness of suicide attempts. Depress Anxiety. 2006;23(1):34-41

Hantouche E, Angst J, Azorin J-M. Explained factors of suicide attempts in major depression. J Affect Disord. 2010;127(1-3):305-308

Aaronson ST, Sears P, Ruvuna F et al. Am J Psychiatry. 2017 Jul 1;174(7):640-648. doi: 10.1176/appi.ajp.2017.16010034. Epub 2017 Mar 31

Decision Memo for Vagus Nerve Stimulation (VNS) for Treatment Resistant Depression (TRD) (CAG-00313R2)

LivaNova 9

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:

LivaNova

	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:

*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] 4/23/2020 Scott T. Aaronson MD

Date *Print Name*

So we may contact you regarding your presentation, please provide the following:

Email Address: saaronson@sheppardpratt.org

Phone Number: 410-938-3125

Comments to WA Healthcare Authority: Vagus Nerve Stimulation for Treatment Resistant Depression

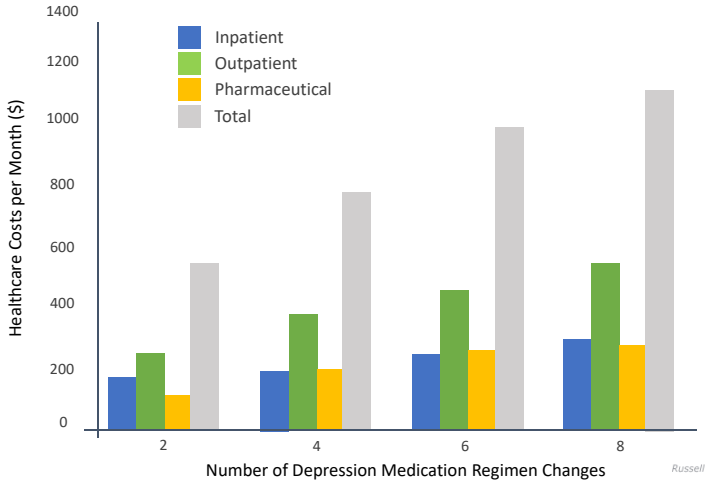
Scott T. Aaronson, MD
Director, Clinical Research Programs
Sheppard Pratt Health System

May 15, 2020
Submitted: April 24, 2020

The Problem of Treatment Resistant Depression

- One third of patients with depression do not respond to at least **two** adequate trials of antidepressants
- Half of those patients do not respond to at least **four** adequate trials of antidepressants
- There are **no** antidepressant trials showing efficacy for those patients with four or more treatment failures
- The data we will show you look at patients who failed an average of **eight** antidepressants.
- These patients are severely impaired, chronically ill, most often disabled by their depression. Their morbidity expenses account for 40% of the $100B annual expense of depression in the US
- We have little to offer these patients

Healthcare Utilization Increases With Greater Degrees of Treatment Resistance



Russell JM, et al. J Clin Psychiatry. 2004;65:341-347.

3

D-23 Study - History and Study Design

Objective

Follow clinical course and outcome for TRD patients treated with and without adjunctive VNS Therapy (requirement of FDA for approval)

5 Years

- **Observational study of unipolar or bipolar depression.**
- **500 VNS + TAU *vs.* 300 TAU**
- **Treated at same medical centers**

Patient Choice

- **Subjects permitted to choose between VNS and TAU at screening**

D-21

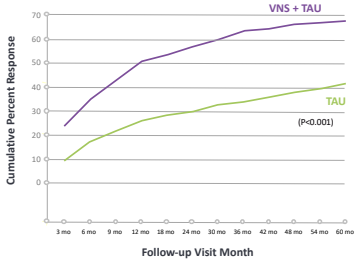
- **Pts from completed D-21 dose finding study could enter**
- **All received VNS and entered the VNS Group**

Aaronson et al. American Journal of Psychiatry 2017

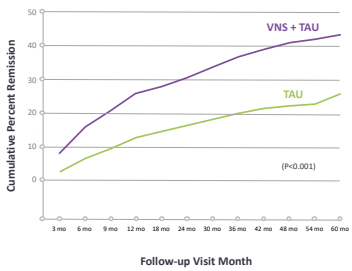
4

D23 Study
Significant Improvement in Response and Remission

Primary Endpoint – First Time Response Rate based on MADRS



Secondary Endpoint – First Time Remission Rate based on MADRS (≤9)



Cumulative Response Rate at 5 years:

- **67.6%** for VNS Therapy
- **40.9%** for TAU

Cumulative Remission Rate at 5 years:

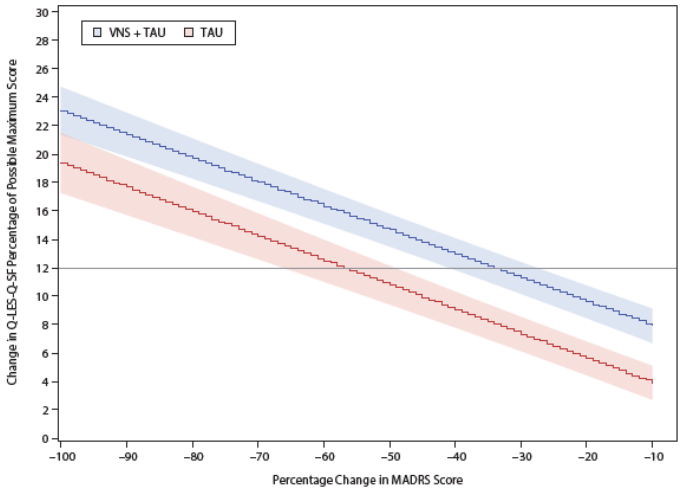
- **43.3%** for VNS Therapy
- **25.7%** for TAU

Aaronson et al. American Journal of Psychiatry 2017

5

Quality of Life Relationship with Depression Reduction

Percentage Change in MADRS Score From Baseline for VNS + TAU and TAU Plotted Against Estimated Change (With 95% Confidence Band) in Q-LES-Q-SF Percentage Maximum Possible Score From Baseline



The horizontal line = clinically significant change in Q-LES-Q-SF percentage of possible maximum score.

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, TAU = treatment as usual (any antidepressant treatment[s]), VNS = vagus nerve stimulation, VNS + TAU = adjunctive VNS.

Conway CR, Kumar A, Xiong W, et al., 2018, *J Clinical Psychiatry*, August 2018.

Why it is important for your patients to have access to VNS therapy

- Few patients achieve response or remission after 4 adequate trials of standard treatment
- Treatment resistant depression is associated with a high risk of suicide
- Patients whose depression is difficult to treat are costly to the health system and few effective and safe treatments are available
- VNS therapy is FDA-approved in a clearly identifiable population; those who have symptoms despite $\varepsilon 4$ antidepressant treatments
- Adding VNS therapy to standard treatment has been shown in long term studies to significantly improve response, remission and reduce suicidality in both randomized trials and real-world studies.
- Compliance with VNS therapy is high, and side-effect are mild and tolerable for most patients.

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:

#5 LivaNova contributes to my research on Vagus Nerve Stimulation for Refractory Depression

#6 LivaNova has sponsored travel to present before Medicare

	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: _____

*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] 4/22/20

Signature *Date*

[redacted]

Print Name

So we may contact you regarding your presentation, please provide the following:

Email Address: conwaycre wustl.edu

Phone Number: [redacted]

Chronic Vagus Nerve Stimulation Significantly Improves Quality of Life in Treatment-Resistant Major Depression

Conway CR, Kumar A, Xiong W, Bunker M, Aaronson ST, Rush AJ., *Journal Clinical Psychiatry*, August 21, 2018. (published online)

VNS Improves Quality of Life in Treatment Resistant Depression (TRD): background

-- Previous studies of VNS in TRD have demonstrated that VNS has positive effects on psychological/functional domains outside of depression, including **reducing anxiety and improving alertness[1-4], lowering pain perception[5], and improving cognition[6-7]**.

-- VNS clinicians noted patient improvement was not captured reliably on standard depression scales. Very low percentage of patients have VNS devices explanted, even though they often do not have "full responses."

-- Given the chronic and difficult-to-treat nature of TRD, a recent trend in psychiatric efficacy outcomes is to place greater emphasis on **overall improvement in functional outcomes**, rather than simply measuring depressive symptoms using classic depression scales (e.g., Hamilton Depression Rating Scale, Montgomery-Asberg Depression Rating Scale)[8].

[1] George MS, et al., 2008; [2]Englot DJ, et al., 2017; [3]Kossoff EH, Pyzik PL. 2004; [4]Shawan A, Bailey C, et al., 2009; [5]Borckardt JJ, Kozel FA, et al.,2005; [6]Clark KB, Naritoku DK, et al.,1999; [7]Sackeim HA, Keilp JG, et al., 2001; [8]Bagby RM, Ryder AG, et al., 2004.

VNS Improves Quality of Life in Treatment Resistant Depression (TRD): the Q-LES-Q-SF

The Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF) is a 14 item, validated, patient self-report scale to measure improvements across a wide range of life areas including physical health, mood, work, economic situation, and social relationships[1]. Each domain is rated as 1-5, for minimal score of 14, maximal score of 70.

Recently, there has been a push to determine if there is a drop in clinical scores which represents the minimal change required to show clinical improvement or the Minimal Clinically Important Difference (MCID).

In a large clinical trial (N=542) of individuals with non–treatment-resistant bipolar depression, **Endicott et al. had determined the MCID for the Q-LES-Q-SF to be an 11.89% max increase from baseline[2]. Or more simply an 8 point increase from baseline (.1189x70=8.323).**

[1]Endicott J, et al., 1993; [2]Endicott J et al., 2007.

VNS Improves Quality of Life in Treatment Resistant Depression (TRD): the CGI-I

In addition to the measurement of quality of life improvement by the Q-LES-Q, another clinician-administered scale, the Clinical Global Impressions-Improvements Scale (CGI-I)[1] was employed. Scores of 1 or 2 were considered treatment "success".

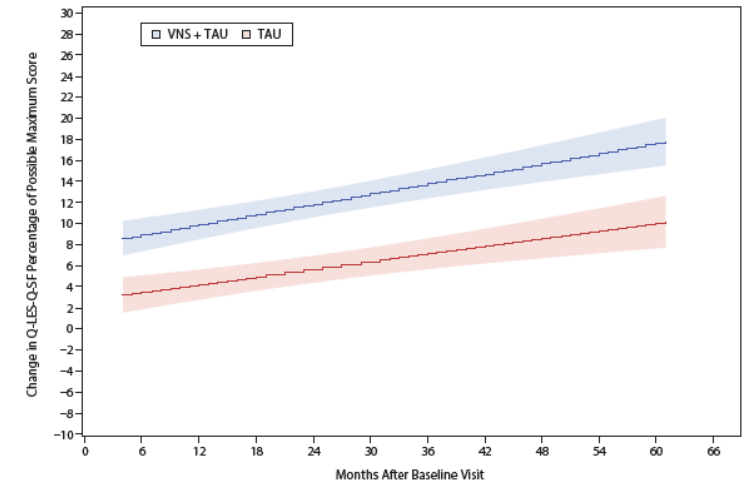
1 = very much improved since baseline
2 = much improved
3 = minimally improved
4 = no change from baseline
5 = minimally worse
6 = much worse
7 = very much worse since the initiation of treatment

[1]Guy W. 1976.

Results

Quality of Life

Months After Baseline Visit Plotted Against Estimated Change (With 95% Confidence Bands) in Q-LES-Q-SF Percentage Maximum Possible Score From Baseline.

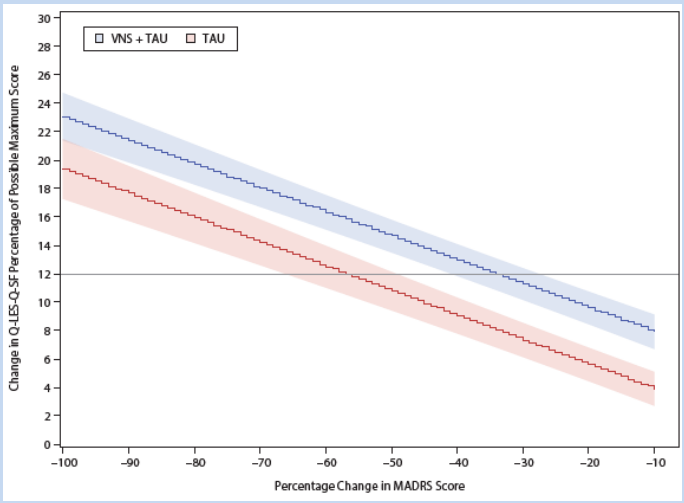


Abbreviations: Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, TAU = treatment as usual (any antidepressant treatment[s]), VNS = vagus nerve stimulation, VNS + TAU = adjunctive VNS and any antidepressant treatments.

Conway CR, Kumar A, Xiong W, et al., 2018, *J Clinical Psychiatry*, August 2018.

Quality of Life Relationship with Depression Reduction

Percentage Change in MADRS Score From Baseline for VNS + TAU and TAU Plotted Against Estimated Change (With 95% Confidence Band) in Q-LES-Q-SF Percentage Maximum Possible Score From Baseline



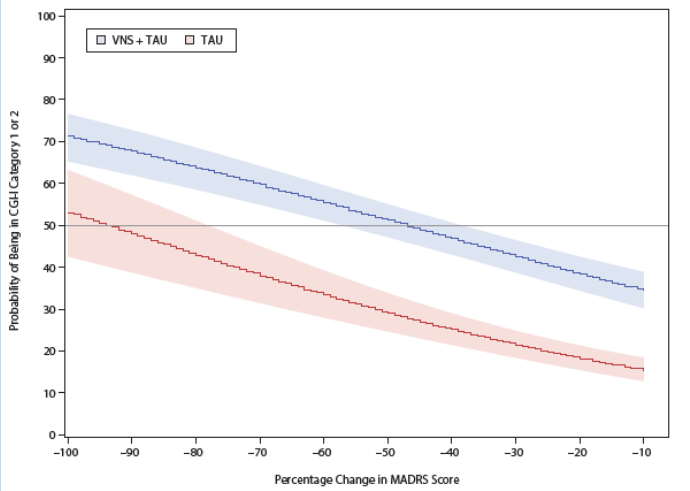
The horizontal line = clinically significant change in Q-LES-Q-SF percentage of possible maximum score.

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, TAU = treatment as usual (any antidepressant treatment[s]), VNS = vagus nerve stimulation, VNS + TAU = adjunctive VNS.

Conway CR, Kumar A, Xiong W, et al., 2018, *J Clinical Psychiatry*, August 2018.

Clinical Global Improvement with Depression Reduction

Estimated Probability (With 95% Confidence Band) of a Patient's Being in CGI-I Category 1 or2 Plotted Against Percentage Change in MADRS Score From Baseline for VNS + TAU and TAU.

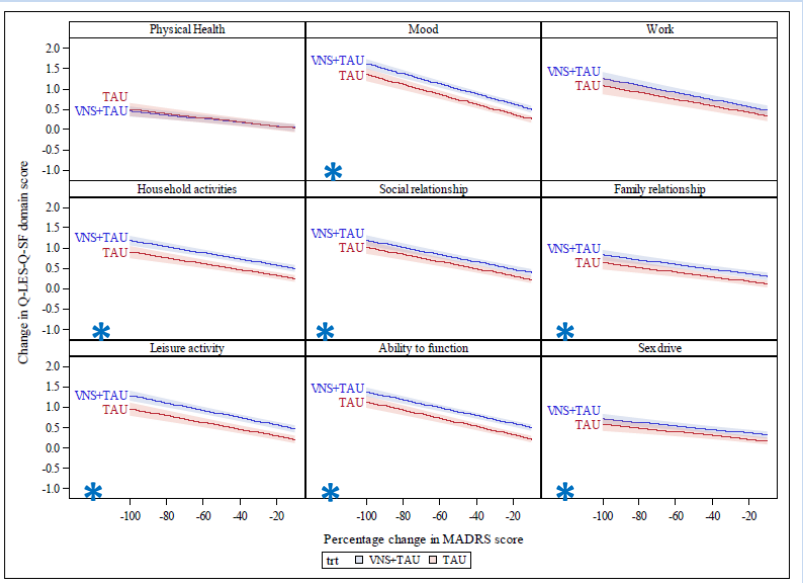


The horizontal lines denotea 50% chance of reaching CGI-I category 1 or 2.

Abbreviations: CGI = Clinical Global Impressions–Improvement scale, MADRS = Montgomery-Asberg Depression Rating Scale, Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire Short Form, TAU = treatment as usual (any antidepressant treatment[s]), VNS = vagus nerve stimulation, VNS + TAU = adjunctive VNS.

Conway CR, Kumar A, Xiong W, et al., 2018, *J Clinical Psychiatry*, August 2018.

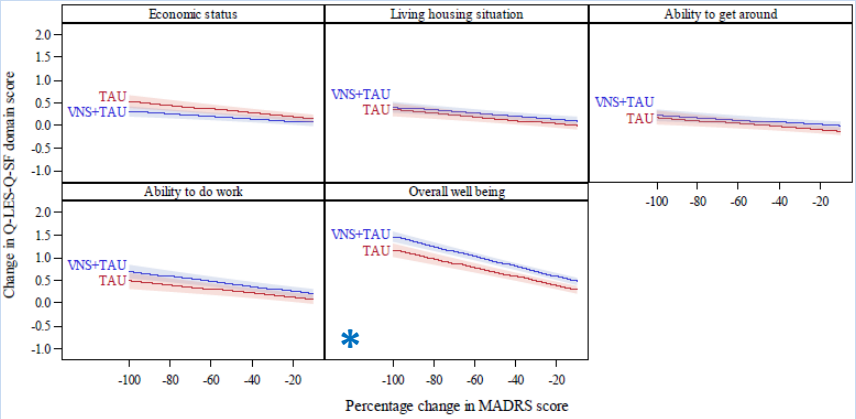
Post Hoc Sub Analysis: Individual Q-LES-Q Domains of Improvement



* Denotes statistically significant (without multiple corrections)

Conway CR, Kumar A, Xiong W, et al., 2018, *J Clinical Psychiatry*, August 2018.

Post Hoc Sub Analysis: Individual Q-LES-Q Domains of Improvement



* Denotes statistically significant (without multiple corrections).

Conway CR, Kumar A, Xiong W, et al., 2018, *J Clinical Psychiatry*, August 2018.

Vagal Nerve Stimulation for Epilepsy and Depression

Washington HTA Committee
May 15, 2020
Beth Shaw, BSc, MSc, and Valerie J. King, MD, MPH

Overview

- Background and Policy Context
- Methods and Search Results
- Summary Findings and Conclusions
- Questions
- Detailed Results, as Requested by the Committee

Source. Creative Commons license.

1

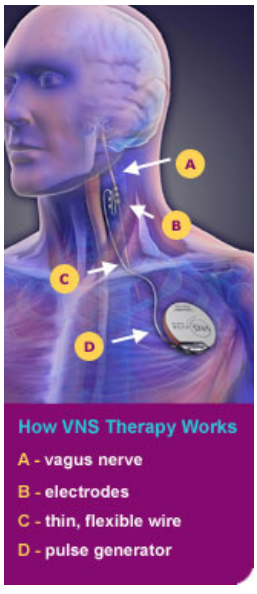
Background and Policy Context

Overview

- Vagal nerve stimulation (VNS) sends electric signals to specific brain structures via the vagus nerve
- A small device (pulse generator) is implanted in the left side of the chest
  - Produces repeating, low-level pulses of electrical current, transmitted via electrical leads along the vagus nerve to the brainstem
- Transcutaneous VNS (tVNS) is a noninvasive alternative
- Mechanism of action is assumed to involve the neuromodulatory action of the vagus nerve, resulting in antiseizure effects, changes in mood, behavior, and cognition

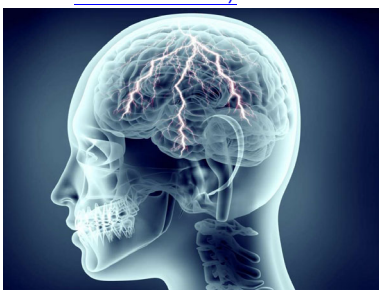
Sources. American Academy of Neurology. 2013; https://www.aan.com/Guidelines/Home/GetGuidelineContent/619. Krahl SE, Clark KB. 2012. doi: 10.4103/2152-7806.103015. Markert MS, Fisher RS. 2019. doi: 10.1080/14737175.2019.1554433. Giordano F, Zicca A, Barba C, Guerrini R, Genitori L. 2017. doi: 10.1111/epi.13678. Ellrich J. 2011. doi: 10.17925/enr.2011.06.04.254. Panebianco M, Rigby A, Weston J, Marson AG. 2015. doi: 10.1002/14651858.CD002896.pub2.

Source. Cyberonics



Overview: Epilepsy

Source. Medical News Today



- VNS may be an option for people whose epilepsy is not adequately controlled with other treatments (pharmacological management or surgery) or for whom surgery is not suitable or possible
  - Many people respond to a first or second trial of an antiseizure medication, but if the second medication fails, odds of response to additional medications are very low
  - People whose epilepsy is not adequately controlled with other treatments are at an increased risk of sudden unexpected death in epilepsy (SUDEP)

Sources. Kwan P, Brodie MJ. 2000. doi: 10.1056/NEJM200002033420503. Tomson T, Nashef L, Ryvlin P. 2008. doi: 10.1016/S1474-4422(08)70202-3.

4

Overview: Treatment-resistant Depression

- VNS may be an option for people with treatment-resistant depression (TRD)
  - Chances of remission are much lower after 2 trials, with around a third of people having no remission after 4 treatment trials
  - Other options include behavioral health therapies (e.g., cognitive behavioural therapy), other stimulation techniques (e.g., electroconvulsive therapy), and novel treatments (e.g., esketamine)

Source. This Photo by Unknown Author is licensed under CC BY

Source. Rush AJ, Trivedi MH, Wisniewski SR, et al. 2006. doi: 10.1176/ajp.2006.163.11.1905.

5

Policy Context: Epilepsy

- In 1997, the U.S. Food and Drug Administration (FDA) approved the use of VNS, through the 510(k) premarket approval process, for:
  - Adjunctive therapy in reducing the frequency of seizures in adults and adolescents older than 12 years of age with partial onset seizures refractory to antiepileptic drugs (AEDs)
- In 2017, the FDA lowered the age of use in children from 12 years to 4 years
- tVNS is not currently FDA-approved for use in epilepsy

Source. Business Wire.

6

Summary of FDA-approved Change in Age for VNS in Epilepsy: Effectiveness in Younger Children

- Based on an analysis of younger and older children and young adults in the pivotal trials used for the initial approval, a Japanese registry, and the Cyberonics Post-Market Surveillance database, the FDA concluded that:
  - VNS is an effective and safe treatment for the reduction of partial onset seizures in pediatric patients 4 to 11 years of age with refractory epilepsy
- Based on the Bayesian hierarchical model, the 12-month responder rate for pediatric patients 4 to 11 years of age with partial onset seizures in the Japan post-approval study was 39% (95% credible interval, 28% to 52%)

7

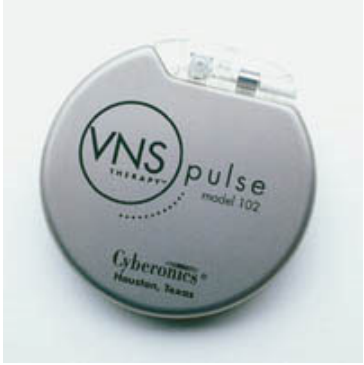
Summary of FDA-approved Change in Age for VNS in Epilepsy: Safety in Younger Children

- No unanticipated adverse device effects observed in pediatric patients 4 to 11 years of age
  - Higher incidence of infection and lead extrusion in patients aged 4 to 11
- Younger patients may have a greater risk for wound infection when compared to adolescents and adults
  - Monitoring for site infection, as well as the avoidance of manipulation of the surgical site post implant in children, should be emphasized
- Overall, treatment-emergent adverse events in patients 4 to 11 years of age were consistent with patients ≥ 12 years of age treated with VNS, and no new risks were identified

8

Policy Context: Depression

- VNS is FDA-approved for:
  - Adjunctive long-term treatment of chronic or recurrent depression for adults who are experiencing a major depressive episode and have not had an adequate response to 4 or more antidepressant treatments
- tVNS is not currently FDA-approved for use in depression



Source. Cyberonics.

9

Policy Context: Washington

- Currently:
  - VNS is a conditionally-covered benefit for the management of epileptic seizures in people aged 12 years or older that have a medically refractory seizure disorder
  - VNS for the treatment of depression is a non-covered benefit
- VNS and tVNS were selected for assessment because of:
  - High concerns about safety
  - Medium concerns about efficacy and costs
  - Changes in FDA approval for epilepsy (i.e., lowering the age in children)

Washington State Health Care Authority

Source. https://www.hca.wa.gov/assets/program/findings_decision_vns_103009[1]_0.pdf

10

Methods

Scope: Epilepsy

Populations	Adults and children (aged 4 and older) with epilepsy
Interventions	• VNS alone, or in combination with TAU (e.g., AEDs) • tVNS alone, or in combination with TAU (e.g., AEDs)
Comparators	• AEDs • Surgery • Other types of brain stimulation (invasive or noninvasive) • Sham VNS[a] • VNS[a] at a subtherapeutic level • No treatment
Outcomes	• Primary outcomes: seizure frequency • Secondary outcomes: seizure cessation; seizure severity; seizure duration; treatment withdrawal; mood or cognitive changes; quality of life • Safety: direct harms (e.g., infection or hoarseness); reimplantation; failure rate • Economic: cost-effectiveness outcomes or cost-utility outcomes
Setting	Any outpatient or inpatient clinical setting in countries categorized as very high on the UN HDI

Note.: [a] VNS also includes tVNS. Abbreviations. AEDs: antiepileptic drugs; UN HDI: United Nations Human Development Index; TAU: treatment as usual; VNS: vagal nerve stimulation.

12

Key Questions: Epilepsy

1. What is the evidence on the efficacy and effectiveness of VNS in adults and children with epilepsy?
2. What direct harms are associated with VNS in adults and children with epilepsy?
3. Do important efficacy/effectiveness outcomes or direct harms of VNS in adults and children with epilepsy vary by:
   a. Patient characteristics (e.g., age, time since diagnosis)
   b. Type of seizure
   c. Duration of treatment
   d. Intensity of treatment
4. What are the cost-effectiveness and other economic outcomes of VNS in adults and children with epilepsy?

13

Scope: Depression

Populations	Adults (aged 18 and older) with TRD
Interventions	• VNS alone, or in combination with TAU (medication or nonpharmacological therapies) • tVNS alone, or in combination with TAU
Comparators	• Antidepressant medication • Nonpharmacological treatments (e.g., CBT) • Other types of invasive or noninvasive brain stimulation (e.g., ECT) • Sham VNS[a] • VNS[a] at a subtherapeutic level • No treatment
Outcomes	• Primary outcomes: depression severity (using a validated tool) • Secondary outcomes: mortality; suicidal ideation; response, remission and duration; treatment withdrawal; compliance with other depression treatments; anxiety; cognitive changes; quality of life; safety: direct harms (e.g., infection or hoarseness); reimplantation; failure rate • Economic: cost-effectiveness outcomes or cost-utility outcomes
Setting	Any outpatient or inpatient clinical setting in countries categorized as very high on the UN HDI

Note. [a] VNS also includes tVNS. Abbreviations. CBT: cognitive behavioral therapy; ECT: electroconvulsive therapy; HDI: Human Development Index; TAU: treatment as usual; tVNS: transcutaneous VNS; UN HDI: United Nations Human Development Index; VNS: vagal nerve stimulation.

Key Questions: Depression

1. What is the evidence on the efficacy and effectiveness of VNS in adults with TRD?
2. What direct harms are associated with VNS in adults with TRD?
3. Do important efficacy/effectiveness outcomes or direct harms of VNS in adults with TRD vary by:
   a. Patient characteristics (e.g., age)
   b. Duration or type of depression (e.g., unipolar vs. bipolar)
   c. Duration of treatment
   d. Intensity of treatment
4. What are the cost-effectiveness and other economic outcomes of VNS in adults with TRD?

15

Eligible Studies: Epilepsy and Depression

- Key Questions 1–4
  - Randomized controlled trials (RCTs)
  - Nonrandomized comparative studies with 10 or more participants in each group
- Additional studies/data for Key Questions 2 and 3 (harms and subgroups)
  - Large, multisite registries with 100 or more participants
  - Databases containing reports of procedure-related harms or device recalls (e.g., FDA MAUDE database, FDA Medical Device Recall database)
- Additional studies/data for Key Question 4
  - Cost-effectiveness studies and other formal comparative economic evaluations

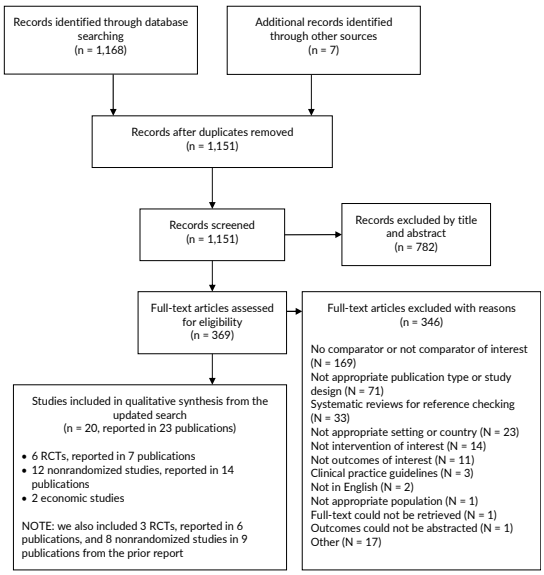
16

Range of Evidence Sources

- Included:
  - Ovid MEDLINE and Epub Ahead of Print, In-Process & Other NonIndexed Citations and Daily
  - Cochrane Library databases (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials)
  - PsycINFO
  - Agency for Healthcare Research and Quality (AHRQ)
  - National Institute for Health and Care Excellence (NICE) – Evidence
  - Veterans Administration Evidence-based Synthesis Program
  - Guideline databases
  - Medicare Coverage Database
  - ClinicalTrials.gov, maintained by the National Library of Medicine at the National Institutes of Health

17

PRISMA Study Flow Diagram



18

Overall Certainty of Evidence

- We assigned a summary judgment for the overall certainty of evidence for each key outcome, based on the GRADE approach

High	Very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect
Moderate	True effect is likely to be close to the estimate of the effect, but there is a possibility that it is different
Low	Little confidence in the estimate of the effect of the intervention on the outcome and the true effect may be substantially different from the estimate of the effect
Very Low	No confidence in the estimate of the effect of the intervention on the outcome and the true effect is likely to be substantially different from the estimate of effect

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation

19

Evidence Review

Summary of the Evidence and Conclusions

Key Findings

- Effectiveness and harms for epilepsy
- Cost-effectiveness for epilepsy
- Effectiveness and harms for depression
- Cost-effectiveness for depression

Effectiveness and Harms: Epilepsy

5 RCTs (in 8 publications)	15 nonrandomized studies	1 RCT
• 4 comparing high- vs. low-stimulation VNS[49-51,80,82,83,87] • 1 comparing VNS plus best medical practice vs. best medical practice[86]	• Varied comparators, including surgery, no treatment, other types of stimulation[55,58,60,63,64,66-69,71-73,75-77]	• Comparing high- vs. low-stimulation tVNS[79]

22

Effectiveness and Harms: Epilepsy
High- vs. Low-Stimulation

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
High-stimulation VNS vs. Low-stimulation VNS			
Outcome: Reduction of 50% or More in Seizure Frequency			
N = 351 3 RCTs[80,82,87]	RR, 1.62; 95% CI, 1.05 to 2.49	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Mean Change in Seizure Frequency			
N = 9 1 RCT[51]	MD, -36.08; 95% CI, -71.34 to -0.82	⊕◯◯◯ VERY LOW	Downgraded 2 levels for risk of bias, and 1 level for imprecision (i.e., wide CIs)
Outcome: Seizure Freedom			
N = 312 2 RCTs[80,87]	1 participant receiving high-stimulation VNS and no participants in the low-stimulation groups became seizure-free	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)

Abbreviations. CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.

23

Effectiveness and Harms: Epilepsy
High- vs. Low-Stimulation

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
High-stimulation VNS vs. Low-stimulation VNS			
Outcome: Treatment Withdrawals			
N = 353 3 RCTs[80,82,87]	RR, 2.56; 95% CI, 0.51 to 12.71	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Voice Alteration or Hoarseness			
N = 312 2 RCTs[80,87]	RR, 2.32; 95% CI, 1.56 to 3.45	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
Outcome: Cough			
N = 312 2 RCTs[80,87]	RR, 1.04; 95% CI, 0.70 to 1.56	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Dyspnea			
N = 312 2 RCTs[80,87]	RR, 2.45; 95% CI, 1.07 to 5.60	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)

Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.

Effectiveness and Harms: Epilepsy
High- vs. Low-Stimulation

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
High-stimulation VNS vs. Low-stimulation VNS			
Outcome: Pain			
N = 312 2 RCTs[80,87]	RR, 1.01; 95% CI, 0.60 to 1.68	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Paresthesias			
N = 312 2 RCTs[80,87]	RR, 0.78; 95% CI, 0.39 to 1.53	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Nausea			
N = 312 2 RCTs[80,87]	RR, 0.72; 95% CI, 0.32 to 1.62	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Headache			
N = 312 2 RCTs[80,87]	RR, 0.90; 95% CI, 0.48 to 1.69	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)

Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.

25

Effectiveness and Harms: Epilepsy
High- vs. Low-Stimulation

- High-stimulation VNS, when compared with low-stimulation VNS:
  - More people having a 50% or more reduction in seizure frequency than low-stimulation VNS (low-quality evidence from 3 RCTs)
  - More effective in reducing mean seizure frequency than low-stimulation VNS (very-low-quality evidence from 1 RCT)
  - Both had very low rates of seizure freedom (low-quality evidence from 2 RCTs)
  - Similar number of withdrawals (very-low-quality evidence from 3 RCTs)
  - Higher levels of voice alteration or hoarseness (moderate-quality evidence from 2 RCTs)
  - Higher rates of dyspnea (low-quality evidence from 2 RCTs)
  - Similar rates of cough, pain, paresthesias, nausea, and headache (very-low-quality evidence from 2 RCTs)

26

Effectiveness and Harms: Epilepsy
VNS vs. Treatment as Usual

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
VNS vs. Treatment as Usual or Ongoing Medication			
Outcome: Reduction of 50% or More in Seizure Frequency			
N = 112 1 RCT[86]	RR, 1.53; 95% CI, 0.63 to 3.74	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., wide CIs)
Outcome: Seizure Frequency (various measures)			
N = 216 4 NRSs[58,63,64,66]	VNS is associated with greater improvements in seizure frequency than treatment as usual or ongoing medication	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Seizure Freedom			
N = 216 4 NRSs[58,63,64,66]	VNS does not appear to be associated with higher rates of seizure freedom than treatment as usual or ongoing medication	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)

Note. Nonrandomized studies start at LOW in the GRADE framework. Abbreviations. CI: confidence interval; NRS: nonrandomized study; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.

27

Effectiveness and Harms: Epilepsy
VNS vs. Treatment as Usual

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
VNS vs. Treatment as Usual			
Outcome: Treatment Withdrawals			
N = 112 1 RCT[86]	RR, 0.84; 95% CI, 0.59 to 1.20	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Voice Alteration or Hoarseness			
N = 112 1 RCT[86]	RR, 18.24; 95% CI, 0.44 to 750.38	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Cough			
N = 112 1 RCT[86]	Not reported		
Outcome: Dyspnea			
N = 112 1 RCT[86]	Not reported		

Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.

Effectiveness and Harms: Epilepsy
VNS vs. Treatment as Usual

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
VNS vs. Treatment as Usual			
Outcome: Pain			
N = 112 1 RCT[86]	RR, 7.51; 95% CI, 0.16 to 357.94	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Paresthesias			
N = 112 1 RCT[86]	RR, 7.51; 95% CI, 0.16 to 357.94	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Nausea			
N = 112 1 RCT[86]	Not reported		
Outcome: Headache			
N = 112 1 RCT[86]	RR, 7.51; 95% CI, 0.16 to 357.94	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)

Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.

Effectiveness and Harms: Epilepsy
VNS vs. Treatment as Usual

- VNS, when compared with treatment as usual (TAU) or ongoing medication:
  - Similar rates of response, defined as a 50% or more reduction in seizures (low-quality evidence from 1 RCT)
  - More effective in reducing seizure frequency than TAU or ongoing medication (very-low-quality evidence from 4 NRSs)
  - No higher rates of seizure freedom than TAU or ongoing medication (very-low-quality evidence from 4 NRSs)
  - Similar number of withdrawals as TAU (low-quality evidence from 1 RCT)
  - Similar levels of voice alteration or hoarseness, pain, paresthesias, headache, as TAU (very-low-quality evidence from 1 RCT)
- Laryngeal symptoms (including hoarseness and coughing) and local dysesthesias related to VNS use tended to decrease over time while rates of high-lead impedance tended to increase

30

Effectiveness and Harms: Epilepsy
VNS vs. Surgery

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
VNS vs. Surgery			
Outcome: Seizure Frequency (various measures)			
N = 192 4 NRSs[55,69,72,73]	VNS may be associated with similar improvements in seizure frequency than surgery, but surgery may be more effective for some patients or specific epilepsies	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)
Outcome: Seizure Freedom			
N = 252 5 NRSs[55,58,69,72,73]	Surgery may be associated with higher rates of seizure freedom than VNS, but results are not consistent	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)

Note. Nonrandomized studies start at LOW in the GRADE framework. Abbreviations. NRS: nonrandomized study; VNS: vagal nerve stimulation.

31

Effectiveness and Harms: Epilepsy
VNS vs. Surgery

- VNS, when compared with surgery:
  - Similar effectiveness as surgery in reducing seizure frequency, but this was not consistent across studies (very-low-quality evidence from 4 NRSs)
  - Less effective in reducing seizure freedom than surgery, but this was not consistent across studies (very-low-quality evidence from 5 NRSs)
- No evidence on comparative harms

32

Effectiveness and Harms: Epilepsy
VNS vs. Other Stimulation Techniques

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
VNS vs. Responsive Neurostimulation			
Outcome: Seizure Frequency (various measures)			
N = 73 2 NRSs[60,67]	VNS may be associated with similar improvements in seizure frequency than responsive neurostimulation, but results are not consistent	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)
Outcome: Seizure Freedom			
N = 73 2 NRSs[60,67]	VNS may be associated with similar rates of seizure freedom than responsive neurostimulation, but results are not consistent	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)

Note. Nonrandomized studies start at LOW in the GRADE framework. Abbreviations. NRS: nonrandomized study; RCT: randomized controlled trial; VNS: vagal nerve stimulation.

33

Effectiveness and Harms: Epilepsy
VNS vs. Other Stimulation Techniques

- VNS, when compared with responsive neurostimulation:
  - Similarly effective in reducing seizure frequency, but this was not consistent across studies (very-low-quality evidence from 2 NRSs)
  - Similarly effective in terms of seizure freedom, but results are not consistent (very-low-quality evidence from 2 NRSs)
- No comparative evidence on harms

34

Effectiveness and Harms: Epilepsy
High- vs. Low-Stimulation tVNS

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
High-stimulation tVNS vs. Low-stimulation tVNS			
Outcome: Reduction of 50% or More in Seizure Frequency			
N = 76 1 RCT[79]	RR, 1.05; 95% CI, 0.50 to 2.24	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Seizure Freedom			
N = 76 1 RCT[79]	2.7% in the high-stimulation tVNS group and 7.7% in the low-stimulation groups became seizure free	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Seizure Severity			
N = 76 1 RCT[79]	Mean change in severity score: 1.56, high-stimulation; 0.83, low-stimulation; *P* > .05 between groups	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)

Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

35

Effectiveness and Harms: Epilepsy
High- vs. Low-Stimulation tVNS

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
High-stimulation tVNS vs. Low-stimulation tVNS			
Outcome: Treatment Withdrawals			
N = 76 1 RCT[79]	RR, 1.32; 95% CI, 0.58 to 2.97	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Voice Alteration or Hoarseness			
N = 76 1 RCT[79]	None were observed	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Cough			
N = 76 1 RCT[79]	None were observed	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Dyspnea			
N = 76 1 RCT[79]	Not reported		

Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

36

Effectiveness and Harms: Epilepsy
High- vs. Low-Stimulation tVNS

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
High-stimulation tVNS vs. Low-stimulation tVNS			
Outcome: Pain			
N = 76 1 RCT[79]	RR, 2.11; 95% CI, 0.38 to 11.81	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Paresthesias			
N = 76 1 RCT[79]	Not reported		
Outcome: Nausea			
N = 76 1 RCT[79]	RR, 1.05; 95% CI 0.14 to 7.93	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Headache			
N = 76 1 RCT[79]	RR, 0.90; 95% CI 0.40 to 2.06	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)

Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

37

Effectiveness and Harms: Epilepsy
High- vs. Low-Stimulation tVNS

- High-stimulation tVNS, when compared with low-stimulation tVNS:
  - Similar rates of response, defined as a 50% reduction or more in seizure frequency (very-low-quality evidence from1 RCT)
  - Similar rates of seizure freedom (low-quality evidence from 1 RCT)
  - Similar seizure severity scores (low-quality evidence from 1 RCT)
  - Similar number of withdrawals (very-low-quality evidence, based on 1 RCT)
  - Similar rates of pain, nausea, headache, (very-low-quality evidence from 1 RCT)
  - No participants in either group reported coughing or hoarseness (low-quality evidence from 1 RCT)

38

SUDEP

- Mortality was not a key outcome for this report
- In 1 RCT comparing high- and low-simulation VNS[87]:
  - 1 patient in the high-stimulation group experienced a nonfatal myocardial infarction, resulting in the generator being deactivated and the device removed
- In 1 RCT comparing high- and low-simulation tVNS[79]:
  - 1 patient in the low-stimulation group died of SUDEP, which was not rated as being related to treatment
  - 1 patient had palpitations, rated as possibly or probably treatment-related

39

Effectiveness and Harms by Subgroup: Epilepsy

Prior Cranial Surgery

- People with prior cranial surgery may have lower rates of response at 12 months vs. no prior surgery, but longer-term outcomes appear to be similar[57]

Early vs. Late VNS

- People who are treated earlier with VNS may have better outcomes[65]

40

Cost-Effectiveness: Epilepsy

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
Outcome:			
N = 1 hypothetical cohort 1 cost-utility analysis[88]	VNS was more costly and less effective than other strategies for children with tuberous sclerosis complex who have not responded to 2 or 3 AEDs	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, indirectness (i.e., tuberous sclerosis complex only) and imprecision (i.e., not assessable)
N = 1,536 1 budget impact study[89]	VNS was associated with a reduction in costs over 5 years compared with AEDs alone	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)

Note. Cost-utility analyses started at HIGH and budget impact studies as LOW in the GRADE framework. Abbreviations. AED: antiepileptic drug; VNS: vagal nerve stimulation.

41

Effectiveness and Harms: Depression

2 RCTs (in 3 publications)	3 NRSs (in 6 publications)	1 RCT
• 1 comparing high- vs. low-stimulation VNS[78] • 1 comparing VNS vs. sham VNS[85,84]	• Comparing VNS vs. TAU[56,59,61, 62,70,74]	• Comparing high- vs. low-stimulation tVNS[81]

42

Effectiveness and Harms: Depression
High- vs. Low-Stimulation VNS

Number of Participants (N) Studies	Findings	Certainty of Evidence	Rationale
High-stimulation VNS vs. Low-stimulation VNS			
Outcome: Depression Severity, Measured on the IDS-C			
N = 224 1 RCT[78]	No difference between 3 VNS stimulation protocols	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Suicide			
N = 224 1 RCT[78]	RR, 0.98; 95% CI, 0.06 to 15.51	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Attempted Suicide			
N = 224 1 RCT[78]	RR, 0.56; 95% CI, 0.17 to 1.86	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Response, Defined as 50% Reduction or More, Measured on the MADRS			
N = 224 1 RCT[78]	RR, 1.84; 95% CI, 1.07 to 3.18	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)

Abbreviations. CI: confidence interval; IDS-C: Inventory of Depressive Symptomatology - Clinician version; MADRS: Montgomery-Åsberg Depression Rating Scale; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.

43

Effectiveness and Harms: Depression
High- vs. Low-Stimulation VNS

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
High-stimulation VNS vs. Low-stimulation VNS			
Outcome: Treatment Withdrawals			
N = 224 1 RCT[78]	RR, 0.39; 95% CI, 0.08 to 1.98	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Voice Alteration or Hoarseness			
N = 224 1 RCT[78]	RR, 1.19; 95% CI, 0.95 to 1.49	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Cough			
N = 224 1 RCT[78]	RR, 1.02; 95% CI, 0.56 to 1.86	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Dyspnea			
N = 224 1 RCT[78]	RR, 1.13; 95% CI, 0.68 to 1.88	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)

Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.

44

Effectiveness and Harms: Depression
High- vs. Low-Stimulation VNS

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
High-stimulation VNS vs. Low-stimulation VNS			
Outcome: Pain			
N = 224 1 RCT[78]	RR, 1.65; 95% CI, 0.99 to 2.74	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Paresthesias			
N = 224 1 RCT[78]	RR, 1.24; 95% CI, 0.74 to 2.07	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Nausea			
N = 224 1 RCT[78]	RR, 0.59; 95% CI, 0.21 to 1.65	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Headache			
N = 224 1 RCT[78]	RR, 1.09; 95% CI, 0.52 to 2.27	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)

Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.

45

Effectiveness and Harms: Depression
High- vs. Low-Stimulation VNS

- High-stimulation VNS, when compared with low-stimulation VNS:
  - Did not reduce depression severity (low-quality evidence from 1 RCT)
  - Did not lower rates of suicide or attempted suicide (very-low-quality evidence from 1 RCT)
  - Higher rates of response, defined as 50% MADRS reduction (low-quality evidence from 1 RCT).
  - Similar number of withdrawals (very-low-quality evidence from 1 RCT)
  - Similar levels of voice alteration or hoarseness (low-quality evidence from 1 RCT)
  - Similar rates of cough, dyspnea, pain, paresthesias, nausea, and headache (very-low-quality evidence from 1 RCT)

46

Effectiveness and Harms: Depression
VNS vs. Sham VNS

Number of Participants (N) Studies	Findings	Certainty of Evidence	Rationale
VNS vs. Sham VNS			
Outcome: Depression Severity, Measured on the HRSD			
N = 222 1 RCT[85]	Estimated difference -0.77; 95% CI, -2.34 to 0.80	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
Outcome: Depression Severity, Measured on the IDS-SR			
N = 222 1 RCT[85]	Estimated difference -2.37; 95% CI, -4.78 to 0.03	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
Outcome: Suicide			
N = 235 1 RCT[85]	RR, 2.92; 95% CI, 0.12 to 71.08	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Response, Defined as 50% Reduction or More, Measured on the MADRS			
N = 222 1 RCT[85]	RR, 1.39; 95% CI, 0.70 to 2.78	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)

Abbreviations. CI: confidence interval; HRSD: Hamilton Rating Scale for Depression; IDS-SR: Inventory of Depressive Symptomatology - Self Report version; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.

47

Effectiveness and Harms: Depression
VNS vs. Sham VNS

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
VNS vs. Sham VNS			
Outcome: Treatment Withdrawals			
N = 222 1 RCT[85]	RR, 6.88; 95% CI, 0.36 to 131.58	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Voice Alteration or Hoarseness			
N = 235 1 RCT[85]	RR, 1.79; 95% CI, 1.27 to 2.54	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
Outcome: Cough			
N = 235 1 RCT[85]	RR, 3.10; 95% CI, 1.36 to 7.07	⊕⊕⊕◯ MODERATE	Downgraded 1 level for risk of bias
Outcome: Dyspnea			
N = 235 1 RCT[85]	RR, 1.64; 95% CI, 0.78 to 3.45	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)

Abbreviations. CI: confidence interval; HRSD: Hamilton Rating Scale for Depression; IDS-SR: Inventory of Depressive Symptomatology - Self Report version; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.

48

Effectiveness and Harms: Depression
VNS vs. Sham VNS

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
VNS vs. Sham VNS			
Outcome: Pain			
N = 235 1 RCT[85]	RR, 2.03; 95% CI, 0.88 to 4.70	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Paresthesias			
N = 235 1 RCT[85]	RR, 1.54; 95% CI, 0.63 to 3.75	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Nausea			
N = 235 1 RCT[85]	RR, 2.11; 95% CI, 0.62 to 7.20	⊕◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Headache			
N = 235 1 RCT[85]	Not reported		

Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.

49

Effectiveness and Harms: Depression
VNS vs. Sham VNS

- VNS, when compared with sham VNS:
  - Not associated with reduced depression severity (moderate-quality evidence from 1 RCT)
  - Not associated with lower rates of suicides (very-low-quality evidence from 1 RCT)
  - Similar rates of response, defined as 50% MADRS reduction (very-low-quality evidence from 1 RCT)
  - Similar number of withdrawals (very-low-quality evidence from 1 RCT)
  - Higher levels of voice alteration or hoarseness and cough (moderate-quality evidence from 1 RCT)
  - Similar levels of dyspnea and pain (low-quality evidence from 1 RCT)
  - Similar rates of paresthesias and nausea (very-low-quality evidence from 1 RCT)

Effectiveness and Harms: Depression
VNS vs. Treatment as Usual

Number of Participants (N) Studies	Findings	Certainty of Evidence	Rationale
VNS+TAU vs. TAU			
Outcome: Mean Difference in Reduction of Depressive Symptoms, Measured on the IDS-SR			
N = 329 1 NRS[62]	VNS+TAU was associated with a greater reduction in depressive symptoms than TAU alone; however, the difference may not be clinically meaningful	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Response, Defined as 50% Reduction or More, Measured on the IDS-SR			
N = 329 1 NRS[62]	VNS+TAU was associated with a higher rate of response than TAU alone	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Attempted Suicide or Self-inflicted Injury			
N = 12,853 1 NRS[61]	VNS may be associated with higher rates of attempted suicide or self-inflicted injury, but this may reflect greater severity of depression	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Mortality			
N = 13,648 2 NRS[56,61]	VNS may be associated with lower mortality rates, but study results are not consistent	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency, and imprecision (i.e., not assessable)

Note. Nonrandomized studies start at LOW in the GRADE framework. Abbreviations. IDS-SR: Inventory of Depressive Symptomatology - Self Report version; NRS: nonrandomized study; TAU: treatment as usual; VNS: vagal nerve stimulation.

51

Effectiveness and Harms: Depression
VNS vs. Treatment as Usual

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
VNS vs. TAU			
Outcome: Treatment Withdrawals			
N = 222 1 NRS[56]	Treatment completion rates were higher in the VNS+TAU group than in the TAU group, but formal statistical testing was not conducted	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias and for imprecision (i.e., wide CIs)

Abbreviations. CI: confidence interval; NRS: nonrandomized study; RCT: randomized controlled trial; RR: risk ratio; TAU: treatment as usual; VNS: vagal nerve stimulation.

52

Effectiveness and Harms: Depression
VNS vs. Treatment as Usual

- VNS, when compared with TAU:
  - More effective in reducing depression symptoms than TAU alone (very-low-quality evidence from 1 NRS)
  - May be associated with higher rates of response than TAU alone (very-low-quality evidence from 1 NRS)
  - May be associated with higher rates of attempted suicide or self-inflicted injury, but the evidence is very uncertain and may reflect greater severity of depression in the VNS group (very-low-quality evidence from 1 NRS)
  - May be associated with lower mortality rates, but study results are not consistent (very-low-quality evidence from 2 NRS)
  - Higher study completion rates than TAU (very-low-quality evidence from 1 NRS)

53

Effectiveness and Harms: Depression
tVNS vs. Sham tVNS

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
tVNS vs. Sham tVNS			
Outcome: Depression Severity, Measured on the HRSD			
N = 37 1 RCT[81]	No difference between tVNS and sham VNS	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Depression Severity, Measured on the BDI			
N = 37 1 RCT[81]	tVNS was associated with a clinically meaningful change in depression	⊕⊕◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)

Abbreviations. BDI: Beck Depression Index; HRSD: Hamilton Rating Scale for Depression; RCT: randomized controlled trial; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

54

Effectiveness and Harms: Depression
tVNS vs. Sham tVNS

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
tVNS vs. Sham tVNS			
Outcome: Overall Adverse Events			
N = 37 1 RCT[81]	No adverse events were observed or reported	⊕◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, indirectness (i.e., not reported by specific adverse event), and imprecision (i.e., not assessable)

Abbreviations. RCT: randomized controlled trial; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

55

Effectiveness and Harms: Depression tVNS vs. Sham tVNS

- tVNS, when compared with sham tVNS:
  - May be associated with meaningful changes in depression; however, this effect was not consistently reported across different measurement scales (low-quality evidence from 1 RCT)
  - It is not clear what adverse events are associated with tVNS (very-low-quality evidence from 1 RCT)

56

Effectiveness and Harms by Subgroup: Depression

Prior ECT Treatment	• Patients who had been treated with ECT (regardless of response) had higher response rates than patients in the TAU group[56]
Comorbid Anxiety	• Individuals with comorbid anxiety had similar rates of response to VNS to those without comorbid anxiety disorders[56]
Type of Depression	• The effectiveness of VNS did not appear to differ by type of depression (unipolar vs. bipolar)[56,62,84]
Age	• Mortality rates were significantly lower in the VNS group than the TRD and managed depression groups overall, but not for the subgroup of people under 40 years of age[61]

57

Cost-Effectiveness: Depression

- We did not identify any eligible studies reporting the economic outcomes of VNS or tVNS for depression

58

FDA Reported Harms for Epilepsy and Depression

- 397 entries in the MAUDE database
  - Voluntary, user facility, distributor, and manufacturer reports of adverse events relating to VNS use in the last 5 years
  - Types of adverse events appeared similar to those reported in our eligible studies for epilepsy and depression
- 26 recalls documented in the Medical Device Recall database
  - Errors in impedance measurements
  - Unintended warning messages
  - Miscalculations resulting in inappropriate VNS stimulation (both higher and lower levels of stimulation than expected)
  - Reductions in device and battery longevity
  - Lead fractures

59

Specific Adverse Events: Bradycardia

- In 1 RCT comparing VNS and sham VNS[85]
  - 1 patient experienced bradycardia during surgery in the VNS group
- From the MAUDE database records
  - 9 cases of bradycardia post surgery
  - 3 cases of bradycardia during surgery

60

FDA Medical Device Recall: Class I

- In December 2019, the FDA issued a Class I recall
  - Most serious type of recall, where problems with the recalled devices may cause serious injuries or death
- LivaNova is recalling the VNS Therapy SenTiva Generator System
  - Unintended reset error that causes the system to stop delivering VNS therapy
- Issued guidance to patients and providers
  - Monitoring of VNS effectiveness and level of stimulation
  - Review of programming
  - Information on alternative treatments

61

FDA Medical Device Recall: Update

Device	Class of Recall	Manufacturer	Reason
VNS Therapy Programmer	2	LivaNova USA Inc	False positive warning may occur after: 1) VNS Generator interrogated at 0mA normal output current 2) Generator programmed to non-0mA output current 3) In-session re-interrogation performed. Users instructed to lower output current and widen pulse width. Only system diagnostic testing evaluates output current. Users may conclude device malfunction, could lead to medical/surgical intervention.
VNS Therapy SenTiva Generator Model 1000	2	LivaNova USA Inc	Firm identified a subset of its generators that were sterilized one additional sterilization cycle, which does not meet the firm's quality specifications.
Cyberonics VNS Therapy AspireSR, Model 106 Generator	2	LivaNova USA Inc	This recall is an expansion of Z-3019-2017 and Z-3020-2017, which was initiated to fix the devices premature battery depletion, caused by electrical leakage on the circuit board assemblies of the Models 105 and 106 generators. *Note this recall occurred in November 2018.
Cyberonics VNS Therapy AspireHC Model 105 Generator	2	LivaNova USA Inc	This recall is an expansion of Z-3019-2017 and Z-3020-2017, which was initiated to fix the devices premature battery depletion, caused by electrical leakage on the circuit board assemblies of the Models 105 and 106 generators. *Note this recall occurred in November 2018.
VNS Therapy SenTiva Generator, Model 1000	**1**	**LivaNova USA Inc**	**Certain Model 1000 generators (SN = 100,000) have experienced unexpected device resets, which resulted in disablement of therapy. Fourteen (14) complaints have been reported. Each of the device resets occurred within 60 days of enabling therapy. Once the device is disabled, therapy can be re-enabled, but the device will continue to be susceptible to resets. If a device experiences this issue and is disabled, patients may return to baseline seizure or depressive symptoms.**

62

Clinical Practice Guidelines and Payer Coverage Policies

Clinical Practice Guidelines: Epilepsy

- 6 relevant guidelines

2 good-methodological-quality	1 fair-methodological-quality	3 poor-methodological-quality
• National Institute for Health and Care Excellence (NICE), 2012[93] • Scottish Intercollegiate Guidelines Network (SIGN), 2015[94]	• Task Force Report for the International League Against Epilepsy (ILAE) Commission of Pediatrics, 2015[95]	• Australian Government Medical Services Advisory Committee (MSAC), 2016[91] • Epilepsy Implementation Task Force, 2016[92] • Wirrel et al. on behalf of a North American Consensus Panel, 2017[96]

64

Clinical Practice Guidelines: Epilepsy

NICE and SIGN	•Recommended VNS as adjunctive therapy for adults with drug-resistant epilepsy who are not suitable candidates for surgery
NICE	•Also recommended VNS an adjunctive therapy for children and young people who are refractory to antiepileptic medication, but who are not suitable candidates for resective surgery
NICE stated that VNS is an option for adults and children whose epileptic disorder is dominated by focal seizures (with or without secondary generalization) or generalized seizures	
Task Force Report for the ILAE Commission of Pediatrics	•Recommended that infants with medically refractory seizures who are not suitable candidates for epilepsy surgery may be considered for VNS
Recommendations from other guidelines also supported the use of VNS for adults and children whose seizures do not respond to other therapies (changes in AEDs, surgery, and the ketogenic diet for children)	

65

Clinical Practice Guidelines: Depression

- 5 relevant guidelines

1 good-methodological-quality	3 fair-methodological-quality	1 poor-methodological-quality
• Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, 2014[101]	• Canadian Network for Mood and Anxiety Treatments, 2016[97] • Department of Veterans Affairs, Department of Defense, 2016[98] • Royal Australian and New Zealand College of Psychiatrists, 2015[100]	• Australian Government Medical Services Advisory Committee (MSAC), 2018[99]

66

Clinical Practice Guidelines: Depression

Working Group of the Clinical Practice Guideline on the Management of Depression in Adults	• VNS outside the scope of research discouraged due to the invasive nature of procedure, and uncertainty about efficacy and adverse effects
Department of Veterans Affairs and Department of Defense	• Recommended against offering VNS for patients with major depressive disorder (MDD), including patients with severe TRD, outside of a research setting
Canadian Network for Mood and Anxiety Treatments: Neurostimulation	• VNS as third-line treatment, after repetitive transcranial magnetic stimulation (first-line) and ECT (second-line) for adults with MDD
Royal Australian and New Zealand College of Psychiatrists	• No explicit recommendations on the use of VNS
Australian Government Medical Services Advisory Committee	• Did not support public funding for chronic major depressive episodes, noting concerns about safety, evidence of effectiveness, and uncertainty on cost-effectiveness

67

Payer Policies: Epilepsy and Depression

- Overall, there is a high level of agreement across the coverage determinations
  - Medicare and the 3 commercial payers covering VNS for the management of seizures, but not for depression; covering revision or replacement of the implant or battery
- None of the reviewed policies specified any age restrictions
- Centers for Medicare & Medicaid Services (CMS) will cover the use of VNS for TRD if the patient is registered in a CMS-approved study
- All of the commercial payers we reviewed consider the use of tVNS as experimental and investigational

68

Ongoing Studies: Epilepsy

NCT Number Study Name Study Type	Participants	Treatment Groups	Outcomes	Estimated Enrollment	Primary Completion Date
Epilepsy					
NCT03529045[103] CORE-VNS Prospective registry	Adults and children with drug-resistant epilepsy	VNS only	• Seizure frequency • Seizure severity • Quality of life • Sleep • AED use • Rescue drug use • ED visits • Hospitalization	2,000	December 2026

Abbreviations. AED: antiepileptic drug; ED: emergency department; NCT: U.S. National Clinical Trial; RCT: randomized controlled trial; VNS: vagal nerve stimulation.

69

Ongoing Studies: Depression

NCT Number Study Name Study Type	Participants	Treatment Groups	Outcomes	Estimated Enrollment	Primary Completion Date
Depression					
NCT03320304[104] RESTORE-LIFE Prospective Registry	Adults with difficult-to-treat depression	VNS only	• Depression • Duration of response • Mania • Quality of life • Functional activity • Suicidality • Antidepressant treatment • Adverse events • Cognition • Anxiety	500	December 2023
NCT03887715[105] RECOVER RCT	Adults with TRD	VNS Sham VNS	• Depression • Adverse events • Disability • Quality of life • Global improvement • Suicidality	6,800	August 2022

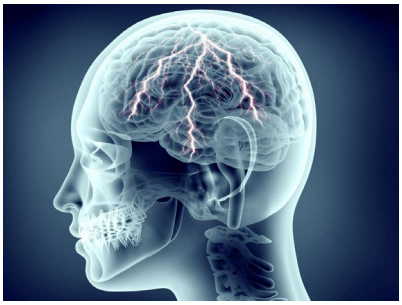
Abbreviations. NCT: U.S. National Clinical Trial; RCT: randomized controlled trial; TRD: treatment-resistant depression; VNS: vagal nerve stimulation.

70

Conclusions

Conclusions: Epilepsy

- VNS is an effective treatment option for people with drug-resistant epilepsy who are not eligible for surgery
- There is a lack of evidence on the cost-effectiveness of VNS for epilepsy
- There is a lack of evidence on the use of tVNS for epilepsy
- Guidelines and commercial coverage policies are supportive of VNS for epilepsy
- Policymakers will need to consider whether the current coverage policy should align the lower age of VNS use with the policy of the FDA



Source. Medical News Today

72

Conclusions: Depression

- VNS may be an effective treatment option for people with TRD who have not responded to other treatments
- There is no evidence on the cost-effectiveness of VNS for TRD
- There is a lack of evidence on tVNS for TRD
- Guidelines and commercial coverage policies are generally not supportive of VNS for TRD
- Policymakers will need to consider whether the current coverage policy should be changed in light of the evidence from this report

Source. This Photo by Unknown Author is licensed under CC BY

73

Questions?

Selected References

Selected References (as numbered in the full report)

49. Dodrill CB, Morris GL. Effects of vagal nerve stimulation on cognition and quality of life in epilepsy. Epilepsy Behav. 2001;2(1):46-53. doi: 10.1006/ebeh.2000.0148.
50. Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. Epilepsy Res. 2000;42(2-3):203-210. doi: 10.1016/s0920-1211(00)00181-9.
51. Landy HJ, Ramsay RE, Slater J, Casiano RR, Morgan R. Vagus nerve stimulation for complex partial seizures: surgical technique, safety, and efficacy. J Neurosurg. 1993;78(1):26-31. doi: 10.3171/jns.1993.78.1.0026.
55. You SJ, Kang HC, Ko TS, et al. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome. Brain Dev. 2008;30(3):195-199. doi: 10.1016/j.braindev.2007.07.013.
56. Aaronson ST, Sears P, Ruvuna F, et al. A 5-year observational study of patients with treatment-resistant depression treated with vagus nerve stimulation or treatment as usual: comparison of response, remission, and suicidality. Am J Psychiatry. 2017;174(7):640-648. doi: 10.1176/appi.ajp.2017.16010034.
57. Amar AP, Apuzzo ML, Liu CY. Vagus nerve stimulation therapy after failed cranial surgery for intractable epilepsy: results from the vagus nerve stimulation therapy patient outcome registry. Neurosurgery. 2004;55(5):1086-1093. doi: 10.1227/01.neu.0000141073.08427.76.
58. Boon P, D'Have M, Van Walleghem P, et al. Direct medical costs of refractory epilepsy incurred by three different treatment modalities: a prospective assessment. Epilepsia. 2002;43(1):96-102. doi: 10.1046/j.1528-1157.2002.40100.x.

76

Selected References (as numbered in the full report)

59. Conway CR, Kumar A, Xiong W, Bunker M, Aaronson ST, Rush AJ. Chronic vagus nerve stimulation significantly improves quality of life in treatment-resistant major depression. J Clin Psychiatry. 2018;79(5):21. doi: 10.4088/JCP.18m12178.
60. Ellens NR, Elisevich K, Burdette DE, Patra SE. A comparison of vagal nerve stimulation and responsive neurostimulation for the treatment of medically refractory complex partial epilepsy. Stereotact Funct Neurosurg. 2018;96(4):259-263. doi: 10.1159/000492232.
61. Feldman RL, Dunner DL, Muller JS, Stone DA. Medicare patient experience with vagus nerve stimulation for treatment-resistant depression. J Med Econ. 2013;16(1):62-74. doi: 10.3111/13696998.2012.724745.
62. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. Biol Psychiatry. 2005;58(5):364-373. doi: 10.1016/j.biopsych.2005.07.028.
63. Gonen OM, Gandelman-Marton R, Kipervasser S, Neufeld MY. The prognosis of refractory epilepsy patients rejected from epilepsy surgery. Acta Neurol Scand. 2015;131(1):58-62. doi: 10.1111/ane.12311.
64. Harden CL, Pulver MC, Ravdin LD, Nikolov B, Halper JP, Labar DR. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. Epilepsy Behav. 2000;1(2):93-99. doi: 10.1006/ebeh.2000.0046.
65. Helmers SL, Griesemer DA, Dean JC, et al. Observations on the use of vagus nerve stimulation earlier in the course of pharmacoresistant epilepsy: patients with seizures for six years or less. Neurologist. 2003;9(3):160-164. doi: 10.1097/00127893-200305000-00004.

77

Selected References (as numbered in the full report)

66. Hoppe C, Wagner L, Hoffmann JM, von Lehe M, Elger CE. Comprehensive long-term outcome of best drug treatment with or without add-on vagus nerve stimulation for epilepsy: a retrospective matched pairs case-control study. Seizure. 2013;22(2):109-115. doi: 10.1016/j.seizure.2012.11.003.
67. Jamy R, Kaur M, Pizarro D, Toth E, Pati S. Practice trends and the outcome of neuromodulation therapies in epilepsy: A single-center study. Epilepsia Open. 2019;4(3):493-497. doi: 10.1002/epi4.12345.
68. Kawai K, Tanaka T, Baba H, et al. Outcome of vagus nerve stimulation for drug-resistant epilepsy: the first three years of a prospective Japanese registry. Epileptic Disord. 2017;19(3):327-338. doi: 10.1684/epd.2017.0929.
69. Kuba R, Novak Z, Chrastina J, et al. Comparing the effects of cortical resection and vagus nerve stimulation in patients with nonlesional extratemporal epilepsy. Epilepsy Behav. 2013;28(3):474-480. doi: 10.1016/j.yebeh.2013.05.036.
70. Kumar A, Bunker MT, Aaronson ST, et al. Durability of symptomatic responses obtained with adjunctive vagus nerve stimulation in treatment-resistant depression. Neuropsychiatr Dis Treat. 2019;15:457-468. doi: 10.2147/NDT.S196665.
71. McGlone J, Valdivia I, Penner M, Williams J, Sadler RM, Clarke DB. Quality of life and memory after vagus nerve stimulator implantation for epilepsy. Can J Neurol Sci. 2008;35(3):287-296. doi: 10.1017/s0317167100008854.
72. Morrison-Levy N, Go C, Ochi A, et al. Children with autism spectrum disorders and drug-resistant epilepsy can benefit from epilepsy surgery. Epilepsy Behav. 2018;85:200-204. doi: 10.1016/j.yebeh.2018.06.023.

78

Selected References (as numbered in the full report)

73. Nei M, O'Connor M, Liporace J, Sperling MR. Refractory generalized seizures: response to corpus callosotomy and vagal nerve stimulation. Epilepsia. 2006;47(1):115-122. doi: 10.1111/j.1528-1167.2006.00377.x.
74. Rush AJ, Sackeim HA, Marangell LB, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. Biol Psychiatry. 2005;58(5):355-363. doi: 10.1016/j.biopsych.2005.05.024.
75. Ryvlin P, So EL, Gordon CM, et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. Epilepsia. 2018;59(3):562-572. doi: 10.1111/epi.14002.
76. Sherman EM, Connolly MB, Slick DJ, Eyrl KL, Steinbok P, Farrell K. Quality of life and seizure outcome after vagus nerve stimulation in children with intractable epilepsy. J Child Neurol. 2008;23(9):991-998. doi: 10.1177/0883073808315417.
77. Van Lierde K, Kryshtopava M, Gadeyne S, et al. Impact of vagal nerve stimulation on objective vocal quality, a pilot study. J Voice. 2015;29(6):777 e779-715. doi: 10.1016/j.jvoice.2015.01.010.
78. Aaronson ST, Carpenter LL, Conway CR, et al. Vagus nerve stimulation therapy randomized to different amounts of electrical charge for treatment-resistant depression: acute and chronic effects. Brain Stimul. 2013;6(4):631-640. doi: 10.1016/j.brs.2012.09.013.
79. Bauer S, Baier H, Baumgartner C, et al. Transcutaneous vagus nerve stimulation (tVNS) for treatment of drug-resistant epilepsy: a randomized, double-blind clinical trial (cMPsE02). Brain Stimul. 2016;9(3):356-363. doi: 10.1016/j.brs.2015.11.003.
80. Handforth A, DeGiorgio CM, Schachter SC, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology. 1998;51(1):48-55. doi: 10.1212/wnl.51.1.48.

79

Selected References (as numbered in the full report)

81. Hein E, Nowak M, Kiess O, et al. Auricular transcutaneous electrical nerve stimulation in depressed patients: a randomized controlled pilot study. J Neural Transm (Vienna). 2013;120(5):821-827. doi: 10.1007/s00702-012-0908-6.
82. Klinkenberg S, Aalbers MW, Vles JS, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. Dev Med Child Neurol. 2012;54(9):855-861. doi: 10.1111/j.1469-8749.2012.04305.x.
83. Klinkenberg S, van den Bosch CN, Majoie HJ, et al. Behavioural and cognitive effects during vagus nerve stimulation in children with intractable epilepsy - a randomized controlled trial. Eur J Paediatr Neurol. 2013;17(1):82-90. doi: 10.1016/j.ejpn.2012.07.003.
84. Nierenberg AA, Alpert JE, Gardner-Schuster EE, Seay S, Mischoulon D. Vagus nerve stimulation: 2-year outcomes for bipolar versus unipolar treatment-resistant depression. Biol Psychiatry. 2008;64(6):455-460. doi: 10.1016/j.biopsych.2008.04.036.
85. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. Biol Psychiatry. 2005;58(5):347-354. doi: 10.1016/j.biopsych.2005.05.025.
86. Ryvlin P, Gilliam FG, Nguyen DK, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. Epilepsia. 2014;55(6):893-900. doi: 10.1111/epi.12611.
87. The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. The Vagus Nerve Stimulation Study Group. Neurology. 1995;45(2):224-230. doi: 10.1212/wnl.45.2.224.

80

Selected References (as numbered in the full report)

88. Fallah A, Weil AG, Wang S, Lewis E, Baca CB, Mathern GW. Cost-utility analysis of competing treatment strategies for drug-resistant epilepsy in children with Tuberous Sclerosis Complex. Epilepsy Behav. 2016;63:79-88. doi: 10.1016/j.yebeh.2016.07.034.
89. Purser MF, Mladsi DM, Beckman A, Barion F, Forsey J. Expected budget impact and health outcomes of expanded use of vagus nerve stimulation therapy for drug-resistant epilepsy. Adv Ther. 2018;35(10):1686-1696. doi: 10.1007/s12325-018-0775-0.
91. Australian Government Medical Services Advisory Committee. Application No. 1358.1 – vagus nerve stimulation (VNS) therapy. 2016; http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1358.1-public. Accessed December 19, 2019.
92. Epilepsy Implementation Task Force; Critical Care Services Ontario. Provincial guidelines for the management of medically-refractory epilepsy in adults and children who are not candidates for epilepsy surgery. 2016; https://www.criticalcareontario.ca/EN/Epilepsy%20Guideline%20Series/Prov%20Guidelines%20for%20Management%20of%20MRE%20in%20Adults%20Children%20not%20candidates%20for%20Surgery_EN.pdf. Accessed December 19, 2019.
93. National Institute for Health and Care Excellence. Epilepsies: diagnosis and management. 2012; https://www.nice.org.uk/guidance/cg137. Accessed December 19, 2019.
94. Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults. 2015; https://www.sign.ac.uk/assets/sign143_2018.pdf. Accessed December 19, 2019.

81

Selected References (as numbered in the full report)

95. Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. Epilepsia. 2015;56(8):1185-1197. doi: 10.1111/epi.13057.
96. Wirrell EC, Laux L, Donner E, et al. Optimizing the diagnosis and management of dravet syndrome: recommendations from a North American consensus panel. Pediatr Neurol. 2017;68:18-34 e13. doi: 10.1016/j.pediatrneurol.2017.01.025.
97. Milev RV, Giacobbe P, Kennedy SH, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 4. Neurostimulation Treatments. Can J Psychiatry. 2016;61(9):561-575. doi: 10.1177/0706743716660033.
98. Department of Veterans Affairs, Department of Defense,. VA/DoD clinical practice guideline for the management of major depressive disorder 2016; https://www.healthquality.va.gov/guidelines/MH/mdd/VADoDMDDCPGFINAL82916.pdf. Accessed December 19, 2019.
99. Australian Government Medical Services Advisory Committee. Application No. 1491 - vagus nerve stimulation (VNS) for chronic major depressive episodes. 2018; http://www.msac.gov.au/internet/msac/publishing.nsf/Content/75B1018C941A6C06CA258164000FFC53/$File/1491%20-%20Final%20PSD.pdf. Accessed December 19, 2019.
100. Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 2015;49(12):1087-1206. doi: 10.1177/0004867415617657.

82

Selected References (as numbered in the full report)

101. Working Group of the Clinical Practice Guideline on the Management of Depression in Adults. Clinical practice guideline on the management of depression in adults. 2014; https://portal.guiasalud.es/wp-content/uploads/2018/12/GPC_534_Depresion_Adulto_Avaliat_compl_en.pdf. Accessed December 19, 2019.
103. ClinicalTrials.gov. NCT03529045. Registry of subjects with drug resistant epilepsy and treated with the VNS therapy system (CORE-VNS). 2018; https://clinicaltrials.gov/ct2/show/NCT03529045. Accessed January 15, 2020.
104. ClinicalTrials.gov. NCT03320304. A study to assess effectiveness and efficiency of VNS therapy in patients with difficult to treat depression (RESTORE-LIFE). 2017; https://clinicaltrials.gov/ct2/show/NCT03320304. Accessed January 15, 2020.
105. ClinicalTrials.gov. NCT03887715. A prospective, multi-center, randomized controlled blinded trial demonstrating the safety and effectiveness of VNS therapy system as adjunctive therapy versus a no stimulation control in subjects with treatment-resistant depression (RECOVER). 2019; https://clinicaltrials.gov/ct2/show/NCT03887715. Accessed January 15, 2020.

83

Additional Slides

Cost-Effectiveness: Epilepsy

- Model inputs
  - All costs are presented in 2016 U.S. dollars
  - Costs per person

Cost Component	Without VNS	With VNS	Assumptions
Device-related Costs			
VNS system device (generator, lead, tunneler)	NA	$36,239	• Assumes each patient receives 1 implant
Procedure for full system placement	NA	$2,661	• Estimate based on 1.5 hours of surgical time
Neurologist visits for programming	NA	$319	• Based on national average cost for neurologist visit for programming • Assumes 3 neurologist visits
Battery (generator) replacement (per person per year)	NA	$2,178	• Sum of battery cost, procedure cost (30 mins of surgical time) and neurologist visit for reprogramming • Assumes 50% of patients will have a battery replacement at 7 years

Abbreviations. NA; not applicable; VNS: vagal nerve stimulation. Source. Adapted from Purser MF, Mladsi DM, Beckman A, Barion F, Forsey J. 2018;35(10):1686-1696. doi: 10.1007/s12325-018-0775-0

85

Cost-Effectiveness: Epilepsy

Cost Component	Without VNS	With VNS	Assumptions
Adverse Event-related Costs			
Neurologist visit for cough (one-time cost)	$0	$40	• Incidence of 37.5% x unit cost of $106
Neurologist visit for voice alteration (one-time cost)	$0	$42	• Incidence of 39.7% x unit cost of $106
Surgical site infection, resulting in device removal (one-time cost)	NA	$95	• Incidence of 2.8% x unit cost of $3,397
AED Costs			
AEDs (cost per year)	$6,502	$6,502	• Average cost calculated as the average daily cost of lacosamide, lamotrigine, topiramate, oxcarbazepine, levetiracetam, carbamazepine, tiagabine • Assumes that 2 AEDs are used per day • Assumes no change in the number of AEDs with VNS

Abbreviations. AED: antiepileptic drugs; NA: not applicable; VNS: vagal nerve stimulation. Source. Adapted from Purser MF, Mladsi DM, Beckman A, Barion F, Forsey J. 2018;35(10):1686-1696. doi: 10.1007/s12325-018-0775-0

86

Clinical Practice Guidelines: Depression Populations

Working Group of the Clinical Practice Guideline on the Management of Depression in Adults	• Adults with TRD, but no clear definition • Care pathway does include behavioural therapies, medication, and review if response not adequate
Department of Veterans Affairs and Department of Defense	• Patients with MDD, including patients with severe TRD
Canadian Network for Mood and Anxiety Treatments: Neurostimulation	• Adults with unipolar depression who have failed 1 at least 1 antidepressant and in whom first-line therapy (rTMS) and second-line therapy (ECT or transcranial direct current stimulation) has failed or is not appropriate
Royal Australian and New Zealand College of Psychiatrists	• People, including children, with MDD, bipolar disorders, and mood disorders with complex presentations
Australian Government Medical Services Advisory Committee	• People with MDD who have not had an adequate response to 4 or more appropriate antidepressant treatments

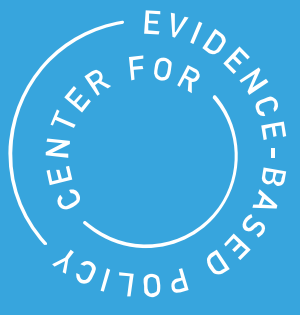
Abbreviations. ECT: electroconvulsive therapy; MDD: major depressive disorder; rTMS: repetitive transcranial magnetic stimulation; TRD: treatment-resistant depression.

87

NCT03887715: RECOVER

- NCT RECOVER
- CMS Decision Memo on VNS for Depression

88



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.

[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

- 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 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);
- Recency (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.

Clinical committee findings and decisions

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?

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.

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.

Discussion document: What are the key factors and health outcomes and what evidence is there? (Applies to the population in the PICO for this review)

Safety outcomes	Importance of outcome	Safety evidence/ confidence in evidence
harms directly related to VNS (e.g., infection or hoarseness)		
reimplantation		
failure rate		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence
Epilepsy		
Primary outcome: • seizure frequency		
Secondary outcomes: • seizure cessation; • seizure severity (measured with a validated tool); • seizure duration; • treatment withdrawal; • mood or cognitive changes (e.g., depression, memory); • quality of life (measured with a validated tool)		
Depression		
Primary outcome: • depression severity (measured using a validated tool)		
Secondary outcomes: • mortality; • suicidal ideation and severity; • response and duration of response;		

Efficacy – effectiveness outcomes	Importance of outcome	Efficacy / Effectiveness evidence
• remission and duration of remission; • treatment withdrawal; • compliance with other depression treatments; • anxiety (measured using a validated tool); cognitive changes (e.g., memory); • quality of life (measured using a validated tool), including sleep		

Cost outcomes	Importance of outcome	Cost evidence
Cost utility outcomes (e.g., cost per QALY, ICER)		
Cost effectiveness (e.g., cost per improved outcome)		

Special population / Considerations outcomes	Importance of outcome	Special populations/ Considerations evidence
Age		
Race		
Gender		
Ethnicity		

For safety:

Is there sufficient evidence that the technology is safe for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For efficacy/ effectiveness:

Is there sufficient evidence that the technology has a meaningful impact on patients and patient care?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

For cost outcomes/ cost-effectiveness:

Is there sufficient evidence that the technology is cost-effective for the indications considered?

Unproven (no)	Less (yes)	Equivalent (yes)	More in some (yes)	More in all (yes)

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.

Next step: proposed findings and decision and public comment

At the next public meeting the committee will review the proposed findings and decision and consider any public comments as appropriate prior to a vote for final adoption of the determination.

1) Based on public comment was evidence overlooked in the process that should be considered?
2) Does the proposed findings and decision document clearly convey the intended coverage determination based on review and consideration of the evidence?

Next step: final determination

Following review of the proposed findings and decision document and public comments:

Final vote

Does the committee approve the Findings and Decisions document with any changes noted in discussion?

If yes, the process is concluded.

If no, or an unclear (i.e., tie) outcome chair will lead discussion to determine next steps.

Medicare Coverage and Guidelines

[From page 78 of final evidence report]

We identified 1 Medicare NCD on the use of VNS.[2] The NCD is currently under review with consideration of new criteria for VNS in depression.[2] We did not identify any Medicare Local Coverage Determinations related to VNS.
The NCD currently states that[2]:

- VNS is reasonable and necessary for patients with medically refractory partial onset seizures for whom surgery is not recommended or for whom surgery has failed.
- VNS is not reasonable and necessary for all other types of seizure disorders which are medically refractory and for whom surgery is not recommended or for whom surgery has failed.

On February 15, 2019, CMS issued an NCD that covers FDA-approved VNS devices for TRD through Coverage with Evidence Development.[2] This requires patients to be entered into a CMS-approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least 1 year (Appendix H) with the possibility of extending the study to a prospective longitudinal study when the CMS-approved, double-blind, randomized placebo-controlled trial has completed enrollment, and there are positive interim findings.[2] Prior to this proposed amendment, CMS stated that VNS was not reasonable and necessary for TRD.[2] The use of VNS for other forms of depression and for use outside of a clinical trial will remain noncovered.[2] At the time of writing this report, only 1 trial is approved by CMS (NCT03887715; Table 22). [102]

CMS also proposed that VNS device replacement be covered, if required due to the end of battery life or any other device-related malfunction, in patients implanted with a VNS device for TRD.[2]

Clinical Practice Guidelines

[From page 72 of final evidence report]

Epilepsy

We identified 6 eligible guidelines on the use of VNS or tVNS for epilepsy (Table 20).[91-96] We included any guideline that met basic eligibility criteria and discussed the use of VNS or tVNS for any type of epilepsy. We assessed 3 clinical practice guidelines[91,92,96] as having poor methodological quality due to serious concerns about the rigor of the evidence development and recommendation generation. We assessed the clinical practice guidelines from Task Force Report for the International League Against Epilepsy (ILAE) Commission of Pediatrics[95] as having fair methodological quality due to concerns about stakeholder involvement and the clarity and presentation. We assessed the clinical practice guidelines from the U.K.'s National Institute for Health and Care Excellence[93] (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) as being of good methodological quality.[94]

Both of the good-methodological-quality guidelines, from NICE and SIGN,[93,94] recommended VNS as adjunctive therapy for adults with drug-resistant epilepsy who are not suitable for surgery. NICE also recommended VNS an adjunctive therapy for children and young people who are refractory to antiepileptic medication but who are not suitable for resective surgery.[93] NICE stated that VNS is an option for adults and children whose epileptic disorder is dominated by focal seizures (with or without secondary generalization) or generalized seizures.[93] SIGN was expected to publish a guideline on the diagnosis and management of epilepsy in children in 2019, but at the time of writing this report, no publication was identified.[94]
The fair-methodological-quality guideline from the Task Force Report for the ILAE Commission of Pediatrics also recommended that infants with medically refractory seizures who are not suitable

candidates for epilepsy surgery may be considered for VNS.[95] However, the Task Force did note there were insufficient data to conclude if there is a benefit from intervention with VNS in infants with seizures and the recommendation was therefore based on expert opinion and standard practice, including receiving optimal level of care at specialist facilities.[95]
Recommendations from the guidelines assessed as poor methodological quality[91,92,96] also support the use of VNS for adults and children who do not achieve adequate benefit from other epilepsy therapies, such as changes in AEDs, surgery, and particularly for children, the ketogenic diet. Only 1 guideline explicitly recommended against the use of tVNS for drug-resistant epilepsy.[92]

Depression

We identified 5 eligible guidelines on the use of VNS or tVNS for depression (Table 21).[97-101] We included any guideline that met basic eligibility criteria and discussed the use of VNS or tVNS for TRD in adults. We assessed 2 clinical practice guidelines[97,99] as having poor-methodological quality due to serious concerns about the rigor of the evidence development and recommendation generation. We assessed the clinical practice guidelines from the Department of Veterans Affairs[98] and the Royal Australian and New Zealand College of Psychiatrists[100] as having fair-methodological quality due to minor concerns about the rigor of the evidence development and recommendation generation and applicability. We assessed the clinical practice guidelines from the Working Group of the Clinical Practice Guideline on the Management of Depression in Adults as having good methodological quality.[101]

The Working Group of the Clinical Practice Guideline on the Management of Depression in Adults,[101] assessed as good methodological quality, in 2014 recommended that the use of VNS for depression outside the scope of research was discouraged due to the invasive nature of the procedure, and uncertainty about its efficacy and adverse effects. A guideline by the Department of Veterans Affairs and Department of Defense,[98] assessed as fair methodological quality, made a similar recommendation, recommending against offering VNS for patients with MDD, including patients with severe TRD, outside of a research setting.[98] However, the other 2 fair-methodological-quality guidelines differed from these recommendations. The Canadian Network for Mood and Anxiety Treatments,[97] in 2016 recommended VNS as a third-line treatment, after repetitive transcranial magnetic stimulation (first-line treatment) and ECT (second-line treatment) for adults with MDD. The Royal Australian and New Zealand College of Psychiatrists[100] in 2015 made no explicit recommendations on the use of VNS for depression. The Australian Government Medical Services Advisory Committee[99] did not support public funding of VNS for chronic major depressive episodes, noting concerns about the comparative safety, the limited evidence of clinical effectiveness, and the resulting uncertainty on the comparative cost-effectiveness of VNS.

Table 20. Clinical Practice Recommendations on VNS for Epilepsy

Organization	Topic	Excerpted Recommendation(s)	Status
Good Methodological Quality			
National Institute for Health and Care Excellence (NICE), 2012[93]	Epilepsies: diagnosis and management	• VNS is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes adults whose epileptic disorder is dominated by focal seizures (with or without secondary generalization) or generalized seizures. • VNS is indicated for use as an adjunctive therapy in reducing the frequency of seizures in children and young people who are refractory to antiepileptic medication but who are not suitable for resective surgery. This includes children and young people whose epileptic disorder is dominated by focal seizures (with or without secondary generalization) or generalized seizures.	Recommendations amended in 2012, assessed as current in 2014, but as needing an update in 2018. New evidence from surveillance indicated that for focal seizures, VNS stimulation using a high-stimulation paradigm is significantly better than low-stimulation in reducing frequency of seizures; therefore the evidence on low- vs. high-stimulation VNS should be considered in the update. The update is due to be published in June 2021.
Scottish Intercollegiate Guidelines Network (SIGN), 2015[94]	Diagnosis and management of epilepsy in adults	• Referral for assessment for neurosurgical treatment should be considered if the epilepsy is drug resistant. ○ Assessment as to suitability for a potentially curative resective procedure should be made before consideration of palliative procedures such as vagus nerve stimulation. • VNS may be considered in adult patients who have been found to be unsuitable for resective surgery.	Recommendations published in 2015, and revised in 2018. A guideline on the diagnosis and management of epilepsy in children was due to be published in 2019, but at the time of writing this report, no publication was identified.
Fair Methodological Quality			
Task Force Report for the ILAE Commission of Pediatrics, 2015[95]	Management of Infantile Seizures	• There are insufficient data to conclude if there is a benefit from intervention with VNS in infants with seizures. • Infants with medically refractory seizures who are not suitable candidates for epilepsy surgery may be considered for VNS (expert opinion and standard practice; optimal level care at tertiary/quaternary facilities) (data are inadequate or conflicting; treatment, test or predictor unproven).	Recommendations published in 2015.

Organization	Topic	Excerpted Recommendation(s)	Status
Poor Methodological Quality			
Australian Government Medical Services Advisory Committee (MSAC), 2016[91]	VNS for refractory epilepsy	• After considering the evidence presented in relation to the comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported MBS funding of VNS therapy for a small patient population with refractory epilepsy and a high unmet clinical need. In this context, MSAC accepted the high cost-effectiveness ratio.	Recommendation made in 2016, with no clear timeframe for updating or surveillance
Epilepsy Implementation Task Force, 2016[92]	Management of medically-refractory epilepsy in adults and children who are not candidates for epilepsy surgery	• Since general neurostimulation devices are less effective than epilepsy surgery, patients with medically-intractable epilepsy should not be considered for such devices until more effective treatment options such as effective surgical resections have been considered. • Patients considered for neurostimulation should have epilepsy refractory to medical therapy and not be candidates for focal resection epilepsy surgery (e.g. seizure onset zone within eloquent cortex, or more than one seizure focus). • tVNS cannot be recommended for the treatment of DRE at the present.	Recommendations published in 2016, with a suggested date for next review of 2018 No updated recommendations were identified at the time of writing this report
Wirrel et al. on behalf of a North American Consensus Panel, 2017[96]	Diagnosis and management of Dravet syndrome	• Before considering any surgery, including VNS, patients must be evaluated at a comprehensive epilepsy center with extensive expertise in Dravet syndrome to ensure other therapies have been maximized • VNS can be considered but only after failure of both first- (clobazam and valproic acid) and second-line (stiripentol, topiramate, and ketogenic diet) treatments. • VNS has a minimal to moderate impact on seizure reduction but is generally less efficacious than the ketogenic diet. • No consensus was reached regarding the efficacy of the magnet to prevent prolonged seizures. • VNS does not significantly benefit development or behavior in most patients.	Recommendations published in 2017, with no clear timeframe for updating or surveillance

Abbreviations. DRE: drug-resistant epilepsy; ILAE: International League Against Epilepsy; MBS: Australian Medicare Benefits Schedule; MSAC: Australian Government Medical Services Advisory Committee; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

Table 21. Clinical Practice Recommendations on VNS for Treatment-Resistant Depression

Organization	Topic	Excerpted Recommendation(s)	Status
Good Methodological Quality			
Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, 2014[101]	Management of depression in adults	• The use of VNS outside the scope of research is discouraged due to the invasive nature of the procedure, uncertainty about its efficacy and adverse effects.	Recommendations published in 2014, with no clear timeframe for updating or surveillance
Fair Methodological Quality			
Canadian Network for Mood and Anxiety Treatments, 2016[97]	Neurostimulation in the management of major depressive disorder in adults	• VNS recommended as third-line treatment, after first-line treatment of repetitive transcranial magnetic stimulation and electroconvulsive therapy as second-line treatment for adults with major depressive disorder.	Recommendations published in 2017, with no clear timeframe for updating or surveillance
Department of Veterans Affairs, Department of Defense, 2016[98]	Management of major depressive disorder	• We recommend against offering VNS for patients with major depressive disorder, including patients with severe treatment-resistant depression, outside of a research setting.	Recommendations published in 2016, with no clear timeframe for updating or surveillance
Royal Australian and New Zealand College of Psychiatrists, 2015[100]	Management of mood disorders	• No explicit recommendations on the use of VNS were made.	Recommendations published in 2015, with no clear timeframe for updating or surveillance
Poor Methodological Quality			
Australian Government Medical Services Advisory Committee (MSAC), 2018[99]	VNS for chronic major depressive episodes	• After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support MBS funding of VNS for chronic major depressive episodes. MSAC accepted that there was a clinical need for more treatment options for this patient population. However, MSAC had concerns regarding the comparative safety, limited evidence of clinical effectiveness, and resulting uncertainty regarding comparative cost-effectiveness for VNS. • MSAC advised that any resubmission should include further clinical effectiveness data from sham-controlled randomized trials and also studies that explore ○ the mechanistic basis for how VNS achieves its antidepressant effects, and ○ whether VNS interacts negatively with ongoing treatment with pharmacological antidepressant agents.	Recommendation made in 2018, with no clear timeframe for updating or surveillance

Abbreviation. MBS: Australian Medicare Benefit Schedule; MSAC: Australian Government Medical Services Advisory Committee; VNS: vagal nerve stimulation.