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:

<table>
<thead>
<tr>
<th>Title</th>
<th>Business Name &amp; Address</th>
<th>Business Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(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:

<table>
<thead>
<tr>
<th>Business Name</th>
<th>Business Address</th>
<th>Business Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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:

<table>
<thead>
<tr>
<th>Received From</th>
<th>Organization Address</th>
<th>Service Performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zogenix, EMERYVILLE, CA.</td>
<td></td>
<td>Scientific Advisory Board</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Source Name &amp; Address</th>
<th>Received By</th>
<th>Source Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childrens University Medical Group</td>
<td>E. J. Novotny, MD</td>
<td>Salary</td>
</tr>
<tr>
<td>4500 Sand Point Way NE, Suite 100, Seattle, WA 98105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of Washington Physicians</td>
<td>Fuki Hisama, MD</td>
<td>Salary</td>
</tr>
<tr>
<td>1959 NE Pacific St, Seattle, WA 98195</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(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.

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.

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.)

<table>
<thead>
<tr>
<th>Lobbyist Name</th>
<th>Business Name</th>
<th>Type</th>
<th>Business Shared</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Provide the information requested in items 5, 6, and 7 below only if:

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:

<table>
<thead>
<tr>
<th>Income Source</th>
<th>Address</th>
<th>Description of Income Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zogenix, EMERYVILLE, CA.</td>
<td>Scientific Advisory Board - Travel expenses</td>
<td></td>
</tr>
</tbody>
</table>
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:

<table>
<thead>
<tr>
<th>Business Name</th>
<th>Business Address</th>
<th>Description of Business</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Name</th>
<th>Description of Service</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Signature: [Redacted] Date: 4/10/2020
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.
Edward J. Novotny, Jr.

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
Edward J. Novotny, Jr.

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.
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.
7. Teaching Attending of the year Department of Neurology Residents – 1997-1998

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)
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
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 (subspecialty Epilepsy) (8/11/2014, #638)

LICENSES:


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

Ver 3/2018 5/37
Edward J. Novotny, Jr.

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.


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 - R21 DA015908 NIH “NMR Studies of Brain Glutamate Turnover in Development” 9/27/2002 – 6/30/2005

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” 2/1/03 – 1/31/2008


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


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

Investigator - 5U01NS053998-03 (Lowenstein) NIH “THE EPILEPSY PHENOME/ GENOME PROJECT (EPGP)” 5/1/2010 – 4/30/2013
Edward J. Novotny, Jr.

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.


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)

Ver 3/2018 7/37
Edward J. Novotny, Jr.

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:


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


27. Chen W, **Novotny EJ**, Zhu X-H, Rothman DL, Shulman RG. Localised 1H NMR


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


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


76. Goncharova II, Zaveri HP, Duckrow RB, Novotny EJ, Spencer SS. Spatial distribution


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


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


Book Chapters:


Electronic Publications:


Abstracts (pre-1990):
1. Sogg RL, Steinman LS, Novotny EJ. Childhood Myasthenia. Presented at the meeting of the Fourth International Congress of Neuro-opthalmology in Hamilton, Bermuda on
June 14, 1982.


**PUBLICATIONS:**

Abstracts (1993 – present):


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


24. Novotny EJ, Rothman DL. Cerebral Glutamate and γ-aminobutyric Acid in Pediatric Epilepsy.


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


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, Spencer SS, and Novotny EJ FAMILIAL PRIMARY HYPMAGNESEMIA 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


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


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


Edward J. Novotny, Jr.


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


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


96. Xiuhua L. Bozarth, Ghayda Mirzaz, Heather Mefford, James Bennett, Fuki Hisama, William Dobyns, Karen Tsuchiya, Edward Novotny. EPIPX gene panel for epileptic encephalopathy. AES 2015


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
Invited Lectures:

6. Boston Children's Hospital - Cerebral amino acid turnover studied by NMR spectroscopy March 1993.
7. Montreal Neurological Institute - Killiam Lecture - 12/14/93
8. Montreal Children’s Hospital – Applications of Multinuclear magnetic resonance spectroscopy to investigations of cerebral metabolism – 12/14/93
10. International Society for Neurochemistry - Kyoto, Japan - 7/7/95
22. Ketogenic diet Workshop – Pediatric Epilepsy Research Center Seattle WA Feb 2001
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
32. Developmental Neuroimaging – Neurology Grand Rounds – UTSW Medical Center Dallas, TX – 4/9/2003
37. Epilepsy Surgery in Childhood – Mitra Hospital, Athens, Greece - 11/18/2006
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.
44. 6th International Epilepsy Colloquium- Corticography in Pediatric Tumors –How can it Help?. Cleveland Clinic, 5/23/2013.
46. British Columbia Epilepsy Symposium. Neuroimaging in Epilepsy, November 1,


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:

Clinical Neurophysiology/Epilepsy Fellows as Director of Pediatric Epilepsy at Yale

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
<table>
<thead>
<tr>
<th>Name</th>
<th>Degree</th>
<th>Institution</th>
<th>Years</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evan Fertig</td>
<td>MD</td>
<td>UMDNJ-New Jersey Med Sch</td>
<td>2003-2005</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Genetics of localization-related epilepsies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Private Practice, Northeast Regional Epilepsy Group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clinical neurophysiology of peripheral nerve disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Associate Professor, Neurology - Yale University, Director Clinical Neurophysiology Laboratory</td>
</tr>
<tr>
<td>Hamada Hamid</td>
<td>DO, MPH</td>
<td>Michigan State University</td>
<td>2006-2008</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diffusion Tensor Imaging in temporal lobe epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Assistant Professor, Neurology – Yale University</td>
</tr>
<tr>
<td>Anjum Hashim</td>
<td>MD</td>
<td>UMDNJ Med School</td>
<td>2005-2006</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Assistant Professor Neurology, UMDNJ</td>
</tr>
<tr>
<td>Heidi Henninger</td>
<td>MD</td>
<td>University of California, San Francisco</td>
<td>1998-2000</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mechanisms of cerebral GABA abnormalities in human epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neurology Practice, Portland ME</td>
</tr>
<tr>
<td>Stephen Holloway</td>
<td>MD</td>
<td>Northwestern University</td>
<td>1994-1996</td>
<td>Postdoctoral Fellow, Clinical Neurophysiology</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Localization of slow wave potentials in human neurological disorders</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Assistant Professor, Neurology – University of Minnesota</td>
</tr>
<tr>
<td>Omotola Hope</td>
<td>MD</td>
<td>Univ of Pennsylvania Sch of Med</td>
<td>2003-2004</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Assistant Professor Neurology, Univ of Texas, Houston</td>
</tr>
<tr>
<td>Linda Huh</td>
<td>MD</td>
<td>University of Toronto</td>
<td>2005-2007</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Assistant Professor Neurology and Pediatrics, BC Children’s Hospital Vancouver, BC</td>
</tr>
<tr>
<td>Ami Katz</td>
<td>MD</td>
<td>Tel Aviv University</td>
<td>1990-1992</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neuroimaging in temporal lobe epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Private Practice, Neurology, CT</td>
</tr>
<tr>
<td>Howard L. Kim</td>
<td>MD</td>
<td>Northwestern University School of Medicine</td>
<td>1990-1992</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Associate Clinical Professor, University of California, Irvine</td>
</tr>
</tbody>
</table>
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 of 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
<table>
<thead>
<tr>
<th>Name</th>
<th>Degree</th>
<th>Institution</th>
<th>Years</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christopher Ransom</td>
<td>MD, PhD</td>
<td>University of Alabama</td>
<td>2007-2010</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td>Assistant Professor, Neurology – University of Washington</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gautami Rao</td>
<td>MD</td>
<td></td>
<td>2004-2006</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td>Private Practice, Westchester, NY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanjay P. Singh</td>
<td>MD</td>
<td>Georgetown University</td>
<td>1999-2001</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td>Professor of Neurology, Chairman, Creighton University</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>David Tinklepaugh</td>
<td>M.D.</td>
<td></td>
<td>2002-2003</td>
<td>Postdoctoral Fellow, Clinical Neurophysiology</td>
</tr>
<tr>
<td>Clinical neurophysiology of peripheral nerve disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private Practice Neurology, Norwich, CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>David Tkeshelashvili</td>
<td>MD</td>
<td>Tbilisi State Medical School</td>
<td>1999-2000</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td>Intraoperative monitoring in human epilepsy</td>
<td></td>
<td></td>
<td>1998-1999</td>
<td>Postdoctoral Fellow, Clinical Neurophysiology</td>
</tr>
<tr>
<td>Dipole localization of the human epileptic focus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private practice, Waterbury, CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>James Thompson,</td>
<td>MD</td>
<td>Medical College of Georgia</td>
<td>1997-1999</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td>Dipole localization of the human temporal lobe focus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurology Practice, Norwalk, CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hajime Tokuno,</td>
<td>MD</td>
<td>George Washington University</td>
<td>1997-1998</td>
<td>Postdoctoral Fellow, Clinical Neurophysiology</td>
</tr>
<tr>
<td>Neuroimaging in stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associate research scientist, Neurology – Yale University</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Megdad Zaatreh,</td>
<td>MD</td>
<td></td>
<td>1999-2001</td>
<td>Postdoctoral Fellow, Epilepsy</td>
</tr>
<tr>
<td>Frontal Lobe epilepsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private Practice, Northeast Regional Epilepsy Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
Vagal nerve stimulation for epilepsy and depression

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

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
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

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?
## Current State Agency Policy on VNS

<table>
<thead>
<tr>
<th></th>
<th>Epilepsy for patients 12 and older</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PEBB/SEBB/UMP</strong></td>
<td>Covered for refractory epilepsy (per HTCC)</td>
<td>Non Covered (per HTCC)</td>
</tr>
<tr>
<td><strong>MEDICAID</strong></td>
<td>Covered for refractory epilepsy (per HTCC)</td>
<td>Non Covered (per HTCC)</td>
</tr>
<tr>
<td><strong>LABOR AND INDUSTRIES</strong></td>
<td>Covered for refractory epilepsy (per HTCC)</td>
<td>Non Covered (per HTCC)</td>
</tr>
</tbody>
</table>

### Current Utilization

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients with VNS procedure/service</th>
<th>Patients per 100,000 members</th>
<th>Average amount, per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>256</td>
<td>15</td>
<td>$3,585</td>
</tr>
<tr>
<td>2018</td>
<td>229</td>
<td>14</td>
<td>$4,162</td>
</tr>
<tr>
<td>2019</td>
<td>283</td>
<td>17</td>
<td>$4,063</td>
</tr>
</tbody>
</table>
### Current Utilization

**PEBB/UMP, 2018-2019: All VNS Procedures**

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
<th>Patients per 100,000 members</th>
<th>Average annual payments, per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018</td>
<td>25</td>
<td>13</td>
<td>$17,182</td>
</tr>
<tr>
<td>2019</td>
<td>17</td>
<td>17</td>
<td>$19,089</td>
</tr>
</tbody>
</table>

**Current Utilization**

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of patients</th>
<th>Average paid amount per procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>43</td>
<td>$8,653</td>
</tr>
<tr>
<td>2018</td>
<td>42</td>
<td>$11,195</td>
</tr>
<tr>
<td>2019</td>
<td>43</td>
<td>$10,007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 4-11 years</th>
<th>Number of patients</th>
<th>Average paid amount per procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017-2019</td>
<td>28</td>
<td>$10,449</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Year (SFY)</th>
<th>Patients</th>
<th>Encounters</th>
<th>Paid amount</th>
<th>Avg. paid amount, per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>43</td>
<td>230</td>
<td>$418,384</td>
<td>$9,730</td>
</tr>
<tr>
<td>2018</td>
<td>26</td>
<td>72</td>
<td>$10,910</td>
<td>$420</td>
</tr>
<tr>
<td>2019</td>
<td>18</td>
<td>38</td>
<td>$3,288</td>
<td>$183</td>
</tr>
</tbody>
</table>

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

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
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

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
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

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.)
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)

Agency Medical Director Concerns

Safety = High
Efficacy = High
Cost = High
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?

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?
**Epilepsy evidence**

RCTs:

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

15 Non-Randomized Trials (NRTs)

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

---

**Epilepsy: Benefits**

**High stim VNS vs low stim (sham) VNS**

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

**Reduction in Seizure Frequency**

**Mean Difference (IV, Fixed, 95% CI)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landt 1993</td>
<td>13.3</td>
<td>13.9</td>
<td>5</td>
<td>12.77</td>
<td>13.88</td>
<td>4</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>5</td>
<td>12.77</td>
<td>13.88</td>
<td>4</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: F = 2.41, df = 2 (P = 0.20), I² = 17%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.20 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mean Difference (IV, Fixed, 95% CI)**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landt 1993</td>
<td>-2.31</td>
<td>16.95</td>
<td>5</td>
<td>12.77</td>
<td>13.88</td>
<td>4</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>5</td>
<td>12.77</td>
<td>13.88</td>
<td>4</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogeneity: F = 2.41, df = 2 (P = 0.20), I² = 17%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.20 (P = 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Epilepsy: Benefits
VNS vs. treatment as usual (TAU)

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>VNS + TAU</th>
<th>TAU</th>
<th>Events Total</th>
<th>Events Total</th>
<th>Weight M.H. Fixed, 95% CI</th>
<th>Risk Ratio M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio 2014</td>
<td>10</td>
<td>54</td>
<td>7</td>
<td>58</td>
<td>100.0%</td>
<td>1.53 (0.83, 3.74)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>54</td>
<td>58</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.94 (P = 0.35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Epilepsy: Benefits
tVNS

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

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High stimulation Events Total</th>
<th>Low stimulation Events Total</th>
<th>Events Total</th>
<th>Weight</th>
<th>Risk Ratio M.H. Fixed, 95% CI</th>
<th>Risk Ratio M.H. Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bravin 2014</td>
<td>10</td>
<td>37</td>
<td>29</td>
<td>20</td>
<td>100.0%</td>
<td>1.05 (0.50, 2.24)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>37</td>
<td>39</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.14 (P = 0.89)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Epilepsy: Harms

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Treatment withdrawal</th>
<th>Hoarseness</th>
<th>Cough</th>
<th>Dyspnea</th>
<th>Pain</th>
<th>Paresthesia</th>
<th>Nausea</th>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNS high vs VNS low</td>
<td>2.5 (0.5–12.7)</td>
<td>2.32 (1.6–34)</td>
<td>1.04 (0.7–1.6)</td>
<td>2.45 (1.1–5.6)</td>
<td>1.01 (0.6–1.7)</td>
<td>1.0 (0.4–1.7)</td>
<td>1.0 (0.4–1.7)</td>
<td>1.0 (0.4–1.7)</td>
</tr>
<tr>
<td>VNS vs TAU</td>
<td>0.84 (0.5–1.2)</td>
<td>1.24 (0.4–750)</td>
<td>7.51 (0.16–358)</td>
<td>7.51 (0.16–358)</td>
<td>7.51 (0.16–358)</td>
<td>7.51 (0.16–358)</td>
<td>7.51 (0.16–358)</td>
<td>7.51 (0.16–358)</td>
</tr>
<tr>
<td>tVNS high vs low</td>
<td>1.32 (0.58–2.97)</td>
<td>1.11 (0.38–11.8)</td>
<td>1.05 (0.14–7.93)</td>
<td>0.9 (0.4–2.06)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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

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
Depression: Benefits
VNS vs Sham

50% reduction in MADRS depression score

Suicide death

Depression: Harms

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Treatment withdrawn</th>
<th>Hoarseness</th>
<th>Cough</th>
<th>Dyspnea</th>
<th>Pain</th>
<th>Paresthesia</th>
<th>Nausea</th>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNS high vs VNS low</td>
<td>0.39</td>
<td>1.19</td>
<td>1.62</td>
<td>1.13</td>
<td>1.65</td>
<td>1.24</td>
<td>0.59</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>(0.08-1.98)</td>
<td>(0.95-1.49)</td>
<td>(0.56-1.86)</td>
<td>(0.68-1.88)</td>
<td>(0.99-2.74)</td>
<td>(0.74-2.07)</td>
<td>(0.21-1.65)</td>
<td>(0.52-2.27)</td>
</tr>
<tr>
<td>VNS vs sham VNS</td>
<td>6.88</td>
<td>1.79</td>
<td>3.10</td>
<td>1.64</td>
<td>2.03</td>
<td>1.54</td>
<td>2.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.36-131)</td>
<td>(1.27-2.54)</td>
<td>(1.36-7.07)</td>
<td>(0.78-3.45)</td>
<td>(0.88-4.70)</td>
<td>(0.63-3.75)</td>
<td>(0.62-7.20)</td>
<td></td>
</tr>
<tr>
<td>VNS vs TAU</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tVNS high vs low</td>
<td>Not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

Differential impact by patient characteristics

- No major distinctions by patient subgroups for either depression or epilepsy
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 ($131K/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.

• VNS for depression:
  – No data

• tVNS for depression or epilepsy:
  – No data
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

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
Recommendation: Transcutaneous Vagal Nerve Stimulation

- tVNS is not covered

Questions?

More Information:
HTA topic webpage

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

**Vagal nerve stimulation for epilepsy and depression**

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

Any unmarked topic will be considered a “Yes”

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

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

_________________________________________________________________________________
_________________________________________________________________________________
_________________________________________________________________________________

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Representation: if representing a person or organization, include the name and</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>funding sources (e.g. member dues, governmental/taxes, commercial products or services, grants from industry or government).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

Signature: ___________________________  Date: 4/23/20  Print Name: Ryder Gwinn, MD

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”

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

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

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

I am 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.

Signature: ___________________________ Date: ____________

Print Name: Catherine J. Hill

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

Email Address: chill@neurosurgery.org

Phone Number: 202-446-2026
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 IVNS 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. 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).
- 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.
- Prior to this proposed amendment, CMS stated that VNS was not reasonable and necessary for TRD. The use of VNS for other forms of depression or for use outside of a clinical trial remain noncovered.
- At the time of writing this report, only 1 trial is approved by CMS (NCT03887715; Table 22).
- 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 IVNS for depression, and the guidelines and coverage policies that mentioned IVNS 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 IVNS 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

![Graphs showing comparison to other neuromodulation techniques.](image)
Comparison to Other Neuromodulation

**Figure 2.** Per protocol analysis of change from baseline in mean IDS-C score by treatment group. Note that the figure prevents only the patients who achieved their assigned dose during the acute phase (up to Week 2).

Long Term Outcomes with Neuromodulation

**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*
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”

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

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

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

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 Signature 4/17/20  Rebecca M. Allen MD MPH

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”

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

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

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.

Signature: [Redacted] 4/17/2020  Joshua Bess MD

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"

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

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

Jaenssen - Speaker (2009); Livio/Loew - Financial investigator for a former research grant; various legal firms; involved individuals; medical records/defendants; current therapy; derivative of上市s

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 [Signature]

[Date: 4/20/20]

Print Name

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

Email Address: [Redacted]

Phone Number: [Redacted]
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”

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

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

LivaNova USA, Incorporated

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.

Signature: _______ Date: 23 April 2020 Print Name: Lorenzo DiCarlo MD

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

Email Address: lorenzo.dicarlo@livanova.com

Phone Number: 415 806 9000
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.
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.

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.
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

VNS for Epilepsy
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

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
VNS for Treatment-Resistant Depression (TRD) - References


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


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

Any unmarked topic will be considered a "Yes"

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

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

Liva Nova

<table>
<thead>
<tr>
<th>Potential Conflict Type</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
<td></td>
<td>✅</td>
</tr>
</tbody>
</table>

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

4/23/2020

Sebastian J. Aaronson MD

Print Name

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

Email Address: searonson@sheppardpratt.org

Phone Number: 410-938-3125
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

![Bar chart showing healthcare costs per month (in dollars) for various types of care (inpatient, outpatient, pharmaceutical, total) across different numbers of depression medication regimen changes (2, 4, 6, 8).](chart)

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)

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

5 Years

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

D23 Study
Significant Improvement in Response and Remission

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

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.

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 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”

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

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

45. **LivaNova contributes to my research on Vagus Nerve Stimulation for Resistant Depression**

46. **LivaNova has sponsored travel to present before Medicare**

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

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 [Signature] 4/22/20 [Date] [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


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)\(^8\).

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, Endicot 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 (\(0.1189 \times 70 = 8.323\)).

\(^1\)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.

**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


---

**Clinical Global Improvement with Depression Reduction**

Estimated Probability (With 95% Confidence Band) of a Patient’s Being in CGI-I Category 1 or 2 Plotted Against Percentage Change in MADRS Score From Baseline for VNS + TAU and TAU.

The horizontal lines denote a 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

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

* Denotes statistically significant (without multiple corrections).

Overview

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

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)


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)

**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

---

**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%)
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 $\geq$ 12 years of age treated with VNS, and no new risks were identified

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
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)

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

<table>
<thead>
<tr>
<th>Populations</th>
<th>Adults and children (aged 4 and older) with epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>• VNS alone, or in combination with TAU (e.g., AEDs)</td>
</tr>
<tr>
<td></td>
<td>• tVNS alone, or in combination with TAU (e.g., AEDs)</td>
</tr>
<tr>
<td>Comparators</td>
<td>• AEDs</td>
</tr>
<tr>
<td></td>
<td>• Surgery</td>
</tr>
<tr>
<td></td>
<td>• Other types of brain stimulation (invasive or noninvasive)</td>
</tr>
<tr>
<td></td>
<td>• Sham VNS(^a)</td>
</tr>
<tr>
<td></td>
<td>• VNS(^a) at a subtherapeutic level</td>
</tr>
<tr>
<td></td>
<td>• No treatment</td>
</tr>
<tr>
<td>Outcomes</td>
<td>• Primary outcomes: seizure frequency</td>
</tr>
<tr>
<td></td>
<td>• Secondary outcomes: seizure cessation; seizure severity; seizure duration; treatment withdrawal; mood or cognitive changes; quality of life</td>
</tr>
<tr>
<td></td>
<td>• Safety: direct harms (e.g., infection or hoarseness); reimplantation; failure rate</td>
</tr>
<tr>
<td></td>
<td>• Economic: cost-effectiveness outcomes or cost-utility outcomes</td>
</tr>
</tbody>
</table>

Setting: Any outpatient or inpatient clinical setting in countries categorized as very high on the UN HDI.

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

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?
Scope: Depression

<table>
<thead>
<tr>
<th>Populations</th>
<th>Adults (aged 18 and older) with TRD</th>
</tr>
</thead>
</table>
| 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?
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

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
PRISMA Study Flow Diagram

- Records identified through database searching (n = 1,168)
- Additional records identified through other sources (n = 7)
- Records after duplicates removed (n = 1,151)
- Records excluded by title and abstract (n = 762)
- Records screened (n = 1,151)
- Full-text articles assessed for eligibility (n = 369)
- Full-text articles excluded with reasons (n = 346)
  - No comparator or not comparator of interest (N = 169)
  - Not appropriate publication type or study design (N = 71)
  - Systematic reviews for reference checking (N = 20)
  - Not appropriate setting or country (N = 33)
  - Not intervention of interest (N = 14)
  - Not outcomes of interest (N = 11)
  - Clinical practice guidelines (N = 3)
  - Not in English (N = 2)
  - Other (N = 17)

Studies included in qualitative synthesis from the updated search (n = 20, reported in 23 publications)

- 6 RCTs, reported in 7 publications
- 12 nonrandomized studies, reported in 14 publications
- 2 economic studies

NOTE: we also included 3 RCTs, reported in 6 publications, and 8 nonrandomized studies in 9 publications from the prior report

Overall Certainty of Evidence

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

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect</td>
</tr>
<tr>
<td>Moderate</td>
<td>True effect is likely to be close to the estimate of the effect, but there is a possibility that it is different</td>
</tr>
<tr>
<td>Low</td>
<td>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</td>
</tr>
<tr>
<td>Very Low</td>
<td>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</td>
</tr>
</tbody>
</table>

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
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)
- 4 comparing high- vs. low-stimulation VNS
  - Studies: 49-51, 80, 82, 83, 87
- 1 comparing VNS plus best medical practice vs. best medical practice
  - Study: 86

#### 15 nonrandomized studies
- Varied comparators, including surgery, no treatment, other types of stimulation
  - Studies: 55, 58, 60, 63, 64, 66-69, 71-73, 75-77

#### 1 RCT
- Comparing high- vs. low-stimulation tVNS
  - Study: 79

---

### Effectiveness and Harms: Epilepsy

#### High- vs. Low-Stimulation

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

**Abbreviations.** CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio; VNS: vagal nerve stimulation.
## Effectiveness and Harms: Epilepsy
### High- vs. Low-Stimulation

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

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

Effectiveness and Harms: Epilepsy
VNS vs. Treatment as Usual

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNS vs. Treatment as Usual or Ongoing Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Reduction of 50% or More in Seizure Frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 112</td>
<td>RR: 1.53; 95% CI: 0.63 to 3.74</td>
<td>□□□□ VERY LOW</td>
<td>Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., wide CIs)</td>
</tr>
<tr>
<td>1 RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Seizure Frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 216</td>
<td>VNS is associated with greater improvements in seizure frequency than treatment as usual or ongoing medication</td>
<td>□□□□ VERY LOW</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)</td>
</tr>
<tr>
<td>4 NRSs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Seizure Freedom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 216</td>
<td>VNS does not appear to be associated with higher rates of seizure freedom than treatment as usual or ongoing medication</td>
<td>□□□□ VERY LOW</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)</td>
</tr>
<tr>
<td>4 NRSs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.
## Effectiveness and Harms: Epilepsy
### VNS vs. Treatment as Usual

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Number of Studies</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VNS vs. Treatment as Usual</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Treatment Withdrawals</td>
<td></td>
<td>N = 112</td>
<td>RR, 0.84; 95% CI, 0.59 to 1.20</td>
<td>⬜⬜️⬜️ LOW Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)</td>
</tr>
<tr>
<td>Outcome: Voice Alteration or Hoarseness</td>
<td>N = 112</td>
<td>RR, 18.24; 95% CI, 0.44 to 750.38</td>
<td>⬜⬜️️️️️ VERY LOW Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
<td></td>
</tr>
<tr>
<td>Outcome: Cough</td>
<td>N = 112</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Dyspnea</td>
<td>N = 112</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

## Effectiveness and Harms: Epilepsy
### VNS vs. Treatment as Usual

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Number of Studies</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VNS vs. Treatment as Usual</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Pain</td>
<td>N = 112</td>
<td>RR, 7.51; 95% CI, 0.16 to 357.94</td>
<td>⬜⬜️️️️️ VERY LOW Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
<td></td>
</tr>
<tr>
<td>Outcome: Paresthesias</td>
<td>N = 112</td>
<td>RR, 7.51; 95% CI, 0.16 to 357.94</td>
<td>⬜⬜️️️️️ VERY LOW Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
<td></td>
</tr>
<tr>
<td>Outcome: Nausea</td>
<td>N = 112</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Headache</td>
<td>N = 112</td>
<td>RR, 7.51; 95% CI, 0.16 to 357.94</td>
<td>⬜⬜️️️️️ VERY LOW Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
<td></td>
</tr>
</tbody>
</table>

**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

Effectiveness and Harms: Epilepsy
VNS vs. Surgery

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNS vs. Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Seizure Frequency (various measures)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 192 4 NRSs55,69,72,73</td>
<td>VNS may be associated with similar improvements in seizure frequency than surgery, but surgery may be more effective for some patients or specific epilepsies</td>
<td>BOOVERY LOW</td>
<td>Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)</td>
</tr>
<tr>
<td>Outcome: Seizure Freedom</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 252 5 NRSs55,58,69,72,73</td>
<td>Surgery may be associated with higher rates of seizure freedom than VNS, but results are not consistent</td>
<td>BOOVERY LOW</td>
<td>Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)</td>
</tr>
</tbody>
</table>

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

Effectiveness and Harms: Epilepsy
VNS vs. Other Stimulation Techniques

<table>
<thead>
<tr>
<th>Outcome: Seizure Frequency (various measures)</th>
<th>Number of Participants (N)</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNS vs. Responsive Neurostimulation</td>
<td>73</td>
<td>VNS may be associated with similar improvements in seizure frequency than responsive neurostimulation, but results are not consistent</td>
<td>![Very Low] (3 stars)</td>
<td>Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)</td>
</tr>
<tr>
<td>N = 73</td>
<td>2 NRSs[^60,67]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome: Seizure Freedom</th>
<th>N = 73</th>
<th>VNS may be associated with similar rates of seizure freedom than responsive neurostimulation, but results are not consistent</th>
<th>![Very Low] (3 stars)</th>
<th>Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 73</td>
<td>2 NRSs[^60,67]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

[^60,67]: References or studies. [32,33]: Page numbers.
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

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

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 76</td>
<td>RR, 1.05; 95% CI, 0.50 to 2.24</td>
<td>✩✩✩✩ VERY LOW</td>
<td>Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
</tr>
</tbody>
</table>

Outcome: Reduction of 50% or More in Seizure Frequency

<table>
<thead>
<tr>
<th>Number of Studies</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 RCT^9</td>
<td>2.7% in the high-stimulation tVNS group and 7.7% in the low-stimulation groups became seizure free</td>
<td>✩✩✩✩ LOW</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)</td>
</tr>
</tbody>
</table>

Outcome: Seizure Freedom

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 76</td>
<td>Mean change in severity score: 1.56, high-stimulation; 0.83, low-stimulation; P &gt; .05 between groups</td>
<td>✩✩✩✩ LOW</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)</td>
</tr>
</tbody>
</table>

Outcome: Seizure Severity

Abbreviations. CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.
### Effectiveness and Harms: Epilepsy High- vs. Low-Stimulation tVNS

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-stimulation tVNS vs. Low-stimulation tVNS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome: Withdrawals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 76</td>
<td>RR, 1.32; 95% CI, 0.58 to 2.97</td>
<td>VERY LOW</td>
<td>Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
</tr>
<tr>
<td>1 RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome: Voice Alteration or Hoarseness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 76</td>
<td>None were observed</td>
<td>LOW</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)</td>
</tr>
<tr>
<td>1 RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome: Cough</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 76</td>
<td>None were observed</td>
<td>LOW</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)</td>
</tr>
<tr>
<td>1 RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Outcome: Dyspnea</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 76</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 RCT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations.** CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.
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 from 1 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)

SUDEP

• Mortality was not a key outcome for this report
• In 1 RCT comparing high- and low-simulation VNS\textsuperscript{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\textsuperscript{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
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\textsuperscript{57}

Early vs. Late VNS

- People who are treated earlier with VNS may have better outcomes\textsuperscript{65}

Cost-Effectiveness: Epilepsy

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Number of Studies</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1 hypothetical cohort 1 cost-utility analysis\textsuperscript{68}</td>
<td></td>
<td>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</td>
<td>(\bigotimes\bigotimes) VERY LOW</td>
<td>Downgraded 1 level each for risk of bias, indirectness (i.e., tuberous sclerosis complex only) and imprecision (i.e., not assessable)</td>
</tr>
<tr>
<td>N = 1,536 1 budget impact study\textsuperscript{69}</td>
<td></td>
<td>VNS was associated with a reduction in costs over 5 years compared with AEDs alone</td>
<td>(\bigotimes\bigotimes) VERY LOW</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)</td>
</tr>
</tbody>
</table>

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.
Effectiveness and Harms: Depression

Effectiveness and Harms: Depression

<table>
<thead>
<tr>
<th>Number of Participants (N) Studies</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-stimulation VNS vs. Low-stimulation VNS</strong></td>
<td>Outcome: Depression Severity, Measured on the IDS-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 224 1 RCT(^78)</td>
<td>No difference between 3 VNS stimulation protocols</td>
<td>低压</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)</td>
</tr>
<tr>
<td><strong>Outcome: Suicide</strong></td>
<td>RR, 0.98; 95% CI, 0.06 to 15.51</td>
<td>极低</td>
<td>Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
</tr>
<tr>
<td>N = 224 1 RCT(^78)</td>
<td>RR, 0.56; 95% CI, 0.17 to 1.86</td>
<td>极低</td>
<td>Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
</tr>
<tr>
<td><strong>Outcome: Attempted Suicide</strong></td>
<td>RR, 1.84; 95% CI, 1.07 to 3.18</td>
<td>低压</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)</td>
</tr>
</tbody>
</table>

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

#### High- vs. Low-Stimulation VNS

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Number of Studies</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-stimulation VNS vs. Low-stimulation VNS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Treatment Withdrawals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 224</td>
<td>1 RCT78</td>
<td>RR, 0.39; 95% CI, 0.08 to 1.98</td>
<td>⬠◯◯◯ VERY LOW</td>
<td>Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
</tr>
<tr>
<td>Outcome: Voice Alteration or Hoarseness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 224</td>
<td>1 RCT78</td>
<td>RR, 1.19; 95% CI, 0.95 to 1.49</td>
<td>⬠◯◯◯ LOW</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)</td>
</tr>
<tr>
<td>Outcome: Cough</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 224</td>
<td>1 RCT78</td>
<td>RR, 1.02; 95% CI, 0.56 to 1.86</td>
<td>⬠◯◯◯ VERY LOW</td>
<td>Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
</tr>
<tr>
<td>Outcome: Dyspnēa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 224</td>
<td>1 RCT78</td>
<td>RR, 1.13; 95% CI, 0.68 to 1.88</td>
<td>⬠◯◯◯ VERY LOW</td>
<td>Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcome: Depression Severity, Measured on the HRSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 222</td>
</tr>
<tr>
<td>1 RCT(^{85})</td>
</tr>
<tr>
<td>Estimated difference -0.77; 95% CI, -2.34 to 0.80</td>
</tr>
<tr>
<td>⏰🕔🕔◯ MODERATE</td>
</tr>
<tr>
<td>Downgraded 1 level for risk of bias</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome: Depression Severity, Measured on the IDS-SR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 222</td>
</tr>
<tr>
<td>1 RCT(^{85})</td>
</tr>
<tr>
<td>Estimated difference -2.37; 95% CI, -4.78 to 0.03</td>
</tr>
<tr>
<td>⏰🕔🕔◯ MODERATE</td>
</tr>
<tr>
<td>Downgraded 1 level for risk of bias</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome: Suicide</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 235</td>
</tr>
<tr>
<td>1 RCT(^{85})</td>
</tr>
<tr>
<td>RR, 2.92; 95% CI, 0.12 to 71.08</td>
</tr>
<tr>
<td>⏰〇〇〇 VERY LOW</td>
</tr>
<tr>
<td>Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome: Response, Defined as 50% Reduction or More, Measured on the MADRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 222</td>
</tr>
<tr>
<td>1 RCT(^{85})</td>
</tr>
<tr>
<td>RR, 1.39; 95% CI, 0.70 to 2.78</td>
</tr>
<tr>
<td>⏰〇〇〇 VERY LOW</td>
</tr>
<tr>
<td>Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CIs: 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.
### Effectiveness and Harms: Depression

#### VNS vs. Sham VNS

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Number of Studies</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome: Treatment Withdrawals</td>
<td></td>
<td>N = 222</td>
<td>RR, 6.88; 95% CI, 0.36 to 131.58</td>
<td>⬤⬤⬤⬤ VERY LOW Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
</tr>
<tr>
<td>VNS vs. Sham VNS</td>
<td>1 RCT&lt;sup&gt;55&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Voice Alteration or Hoarseness</td>
<td></td>
<td>N = 235</td>
<td>RR, 1.79; 95% CI, 1.27 to 2.54</td>
<td>⬤⬤⬤⬤ MODERATE Downgraded 1 level for risk of bias</td>
</tr>
<tr>
<td>VNS vs. Sham VNS</td>
<td>1 RCT&lt;sup&gt;55&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Cough</td>
<td></td>
<td>N = 235</td>
<td>RR, 3.10; 95% CI, 1.36 to 7.07</td>
<td>⬤⬤⬤⬤ MODERATE Downgraded 1 level for risk of bias</td>
</tr>
<tr>
<td>VNS vs. Sham VNS</td>
<td>1 RCT&lt;sup&gt;55&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Dyspnea</td>
<td></td>
<td>N = 235</td>
<td>RR, 1.64; 95% CI, 0.78 to 3.45</td>
<td>⬤⬤⬤◯ LOW Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)</td>
</tr>
<tr>
<td>VNS vs. Sham VNS</td>
<td>1 RCT&lt;sup&gt;55&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.

### Effectiveness and Harms: Depression

#### VNS vs. Sham VNS

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Number of Studies</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome: Pain</td>
<td></td>
<td>N = 235</td>
<td>RR, 2.03; 95% CI, 0.88 to 4.70</td>
<td>⬤⬤⬤◯ LOW Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)</td>
</tr>
<tr>
<td>VNS vs. Sham VNS</td>
<td>1 RCT&lt;sup&gt;55&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Paresthesias</td>
<td></td>
<td>N = 235</td>
<td>RR, 1.54; 95% CI, 0.63 to 3.75</td>
<td>⬤⬤⬤⬤ VERY LOW Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
</tr>
<tr>
<td>VNS vs. Sham VNS</td>
<td>1 RCT&lt;sup&gt;55&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Nausea</td>
<td></td>
<td>N = 235</td>
<td>RR, 2.11; 95% CI, 0.62 to 7.20</td>
<td>⬤⬤⬤⬤ VERY LOW Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)</td>
</tr>
<tr>
<td>VNS vs. Sham VNS</td>
<td>1 RCT&lt;sup&gt;55&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Headache</td>
<td></td>
<td>N = 235</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>VNS vs. Sham VNS</td>
<td>1 RCT&lt;sup&gt;55&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Studies</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNS+TAU vs. TAU</td>
<td></td>
<td>Outcome: Mean Difference in Reduction of Depressive Symptoms, Measured on the IDS-SR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 329</td>
<td>1 NRS52</td>
<td>VNS+TAU was associated with a greater reduction in depressive symptoms than TAU alone; however, the difference may not be clinically meaningful</td>
<td>◁◯◯◯ VERY LOW</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)</td>
</tr>
<tr>
<td>Outcome: Response, Defined as 50% Reduction or More, Measured on the IDS-SR</td>
<td></td>
<td>VNS+TAU was associated with a higher rate of response than TAU alone</td>
<td>◁◯◯◯ VERY LOW</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)</td>
</tr>
<tr>
<td>N = 329</td>
<td>1 NRS52</td>
<td>VNS+TAU vs. TAU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Mortality</td>
<td></td>
<td>VNS may be associated with lower mortality rates, but study results are not consistent</td>
<td>◁◯◯◯ VERY LOW</td>
<td>Downgraded 1 level each for risk of bias, inconsistency, and imprecision (i.e., not assessable)</td>
</tr>
</tbody>
</table>


WA - Health Technology Clinical Committee
Effectiveness and Harms: Depression
VNS vs. Treatment as Usual

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Number of Studies</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNS vs. TAU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Treatment Withdrawals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 222</td>
<td>1 NRS56</td>
<td>Treatment completion rates were higher in the VNS+TAU group than in the TAU group, but formal statistical testing was not conducted</td>
<td>VERY LOW</td>
<td>Downgraded 1 level each for risk of bias and for imprecision (i.e., wide CIs)</td>
</tr>
</tbody>
</table>

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

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)
### Effectiveness and Harms: Depression
tVNS vs. Sham tVNS

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>tVNS vs. Sham tVNS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Depression Severity, Measured on the HRSD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 RCT&lt;sup&gt;81&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No difference between tVNS and sham VNS</td>
<td>☒☒☐☐</td>
<td>LOW</td>
<td>Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)</td>
</tr>
</tbody>
</table>

| Outcome: Depression Severity, Measured on the BDI |          |                        |           |
| N = 37 |          |                        |           |
| 1 RCT<sup>81</sup> |          |                        |           |
| 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.

---

### Effectiveness and Harms: Depression
tVNS vs. Sham tVNS

<table>
<thead>
<tr>
<th>Number of Participants (N)</th>
<th>Findings</th>
<th>Certainty of Evidence</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>tVNS vs. Sham tVNS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome: Overall Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 37</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 RCT&lt;sup&gt;81&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No adverse events were observed or reported</td>
<td>☒☐☐☐</td>
<td>VERY LOW</td>
<td>Downgraded 1 level each for risk of bias, indirectness (i.e., not reported by specific adverse event), and imprecision (i.e., not assessable)</td>
</tr>
</tbody>
</table>

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

---

**Effectiveness and Harms by Subgroup: Depression**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior ECT Treatment</td>
<td>Patients who had been treated with ECT (regardless of response) had higher response rates than patients in the TAU group</td>
</tr>
<tr>
<td>Comorbid Anxiety</td>
<td>Individuals with comorbid anxiety had similar rates of response to VNS to those without comorbid anxiety disorders</td>
</tr>
<tr>
<td>Type of Depression</td>
<td>The effectiveness of VNS did not appear to differ by type of depression (unipolar vs. bipolar)</td>
</tr>
<tr>
<td>Age</td>
<td>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</td>
</tr>
</tbody>
</table>
Cost-Effectiveness: Depression

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

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
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

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
## FDA Medical Device Recall: Update

<table>
<thead>
<tr>
<th>Device</th>
<th>Class of Recall</th>
<th>Manufacturer</th>
<th>Reason</th>
</tr>
</thead>
</table>
| 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 disableness 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. |

## Clinical Practice Guidelines and Payer Coverage Policies
### Clinical Practice Guidelines: Epilepsy

**6 relevant guidelines**

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

---

### 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 as 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)**
Clinical Practice Guidelines: Depression

- **5 relevant guidelines**

<table>
<thead>
<tr>
<th>1 good-methodological-quality</th>
<th>3 fair-methodological-quality</th>
<th>1 poor-methodological-quality</th>
</tr>
</thead>
</table>
| • Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, 2014<sup>1</sup> | • Canadian Network for Mood and Anxiety Treatments, 2016<sup>77</sup>  
• Department of Veterans Affairs, Department of Defense, 2016<sup>78</sup>  
• Royal Australian and New Zealand College of Psychiatrists, 2015<sup>100</sup> | • Australian Government Medical Services Advisory Committee (MSAC), 2018<sup>99</sup> |

---

**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 |
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

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

Ongoing Studies: Epilepsy

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Study Name Study Type</th>
<th>Participants</th>
<th>Treatment Groups</th>
<th>Outcomes</th>
<th>Estimated Enrollment</th>
<th>Primary Completion Date</th>
</tr>
</thead>
</table>
| NCT03529045 | 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 |
## Ongoing Studies: Depression

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

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

## 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

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
Questions?

Selected References
Selected References (as numbered in the full report)


Selected References (as numbered in the full report)


Selected References (as numbered in the full report)


Selected References (as numbered in the full report)


Selected References (as numbered in the full report)


Selected References (as numbered in the full report)


Selected References (as numbered in the full report)


Cost-Effectiveness: Epilepsy

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

<table>
<thead>
<tr>
<th>Cost Component</th>
<th>Without VNS</th>
<th>With VNS</th>
<th>Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device-related Costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VNS system device (generator, lead, tunneler)</td>
<td>NA</td>
<td>$36,239</td>
<td>Assumptions each patient receives 1 implant</td>
</tr>
<tr>
<td>Procedure for full system placement</td>
<td>NA</td>
<td>$2,661</td>
<td>Estimate based on 1.5 hours of surgical time</td>
</tr>
<tr>
<td>Neurologist visits for programming</td>
<td>NA</td>
<td>$319</td>
<td>Based on national average cost for neurologist visit for programming</td>
</tr>
<tr>
<td>Battery (generator) replacement (per person per year)</td>
<td>NA</td>
<td>$2,178</td>
<td>Sum of battery cost, procedure cost (30 mins of surgical time) and neurologist visit for reprogramming</td>
</tr>
</tbody>
</table>

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
### Cost-Effectiveness: Epilepsy

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


### 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.
NCT03887715: RECOVER

- NCT RECOVER
- CMS Decision Memo on VNS for Depression
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 evidence⁴ 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.

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

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

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

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

**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 timeframe; 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)

<table>
<thead>
<tr>
<th>Safety outcomes</th>
<th>Importance of outcome</th>
<th>Safety evidence/ confidence in evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>harms directly related to VNS (e.g., infection or hoarseness)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>reimplantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>failure rate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

- 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

<table>
<thead>
<tr>
<th>Importance of outcome</th>
<th>Efficacy / Effectiveness evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Cost outcomes

<table>
<thead>
<tr>
<th>Importance of outcome</th>
<th>Cost evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost utility outcomes (e.g., cost per QALY, ICER)</td>
<td></td>
</tr>
<tr>
<td>Cost effectiveness (e.g., cost per improved outcome)</td>
<td></td>
</tr>
</tbody>
</table>

### Special population / Considerations outcomes

<table>
<thead>
<tr>
<th>Importance of outcome</th>
<th>Special populations/ Considerations evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
</tbody>
</table>

### For safety:

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

<table>
<thead>
<tr>
<th>Unproven (no)</th>
<th>Less (yes)</th>
<th>Equivalent (yes)</th>
<th>More in some (yes)</th>
<th>More in all (yes)</th>
</tr>
</thead>
</table>

### For efficacy/ effectiveness:

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

<table>
<thead>
<tr>
<th>Unproven (no)</th>
<th>Less (yes)</th>
<th>Equivalent (yes)</th>
<th>More in some (yes)</th>
<th>More in all (yes)</th>
</tr>
</thead>
</table>
For cost outcomes/ cost-effectiveness:

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

<table>
<thead>
<tr>
<th>Unproven (no)</th>
<th>Less (yes)</th>
<th>Equivalent (yes)</th>
<th>More in some (yes)</th>
<th>More in all (yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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. The NCD is currently under review with consideration of new criteria for VNS in depression. We did not identify any Medicare Local Coverage Determinations related to VNS.

The NCD currently states that:

- 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. 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. Prior to this proposed amendment, CMS stated that VNS was not reasonable and necessary for TRD. The use of VNS for other forms of depression and for use outside of a clinical trial will remain noncovered. At the time of writing this report, only 1 trial is approved by CMS (NCT03887715; Table 22).

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.

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). 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 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 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 (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) as being of good methodological quality. Both of the good-methodological-quality guidelines, from NICE and SIGN, 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. 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. 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. 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. 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.

Recommendations from the guidelines assessed as poor methodological quality 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.

**Depression**

We identified 5 eligible guidelines on the use of VNS or tVNS for depression (Table 21). 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 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 and the Royal Australian and New Zealand College of Psychiatrists 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.

The Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, 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, 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. However, the other 2 fair-methodological-quality guidelines differed from these recommendations. The Canadian Network for Mood and Anxiety Treatments, 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 in 2015 made no explicit recommendations on the use of VNS for depression. The Australian Government Medical Services Advisory Committee 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

<table>
<thead>
<tr>
<th>Organization</th>
<th>Topic</th>
<th>Excerpted Recommendation(s)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good Methodological Quality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 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.  
  o 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. |
<table>
<thead>
<tr>
<th>Organization</th>
<th>Topic</th>
<th>Excerpted Recommendation(s)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian Government Medical Services Advisory Committee (MSAC), 2016&lt;sup&gt;91&lt;/sup&gt;</td>
<td>VNS for refractory epilepsy</td>
<td>• 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.</td>
<td>Recommendation made in 2016, with no clear timeframe for updating or surveillance</td>
</tr>
</tbody>
</table>
| Epilepsy Implementation Task Force, 2016<sup>92</sup>                         | 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<sup>96</sup> | 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-line (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

<table>
<thead>
<tr>
<th>Organization</th>
<th>Topic</th>
<th>Excerpted Recommendation(s)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good Methodological Quality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, 2014101</td>
<td>Management of depression in adults</td>
<td>• 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.</td>
<td>Recommendations published in 2014, with no clear timeframe for updating or surveillance</td>
</tr>
<tr>
<td><strong>Fair Methodological Quality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canadian Network for Mood and Anxiety Treatments, 201697</td>
<td>Neurostimulation in the management of major depressive disorder in adults</td>
<td>• 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.</td>
<td>Recommendations published in 2017, with no clear timeframe for updating or surveillance</td>
</tr>
<tr>
<td>Department of Veterans Affairs, Department of Defense, 201698</td>
<td>Management of major depressive disorder</td>
<td>• We recommend against offering VNS for patients with major depressive disorder, including patients with severe treatment-resistant depression, outside of a research setting.</td>
<td>Recommendations published in 2016, with no clear timeframe for updating or surveillance</td>
</tr>
<tr>
<td>Royal Australian and New Zealand College of Psychiatrists, 2015100</td>
<td>Management of mood disorders</td>
<td>• No explicit recommendations on the use of VNS were made.</td>
<td>Recommendations published in 2015, with no clear timeframe for updating or surveillance</td>
</tr>
<tr>
<td><strong>Poor Methodological Quality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Australian Government Medical Services Advisory Committee (MSAC), 201899     | 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  
    o the mechanistic basis for how VNS achieves its antidepressant effects, and  
    o 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.