

Health Technology Clinical Committee

Date: June 12, 2020
Time: 8:00 a.m. – 12:30 p.m.
Location: Webinar
Adopted: Pending

Meeting materials and transcript are available on the [HTA website](#).

Draft HTCC Minutes

Members present: John Bramhall, MD, PhD, Janna Friedly, MD; Chris Hearne, BSN, DNP, MPH; Conor Kleweno, MD; Laurie Mischley, ND, MPH, PhD; Sheila Rege, MD MPH; Seth Schwartz, MD, MPH; Mika Sinanan, MD, PhD; Kevin Walsh, MD; Tony Yen, MD

Clinical expert: Paul A. Manner, MD

HTCC Formal Action

- 1. Call to order:** Dr. Rege, chair, called the meeting to order; members present constituted a quorum.
- 2. HTA program updates:** Josh Morse, program director, presented HTCC meeting protocols and guidelines, a high-level overview of the HTA program, how to participate in the HTCC process, and upcoming topics.
- 3. Previous meeting business:**

May 15, 2020 meeting minutes: Draft minutes reviewed. Motion made and seconded to approve the minutes as written.

Action: Ten committee members approved the May 15, 2020 meeting minutes.

- 4. Stem cell therapy for musculoskeletal conditions**

Clinical expert: The chair introduced Paul A. Manner, MD, Professor, Department of Orthopaedics and Sports Medicine University of Washington School of Medicine.

Agency utilization and outcomes: Jason Fodeman, MD, MBA, Associate Medical Director, Department of Labor and Industries, presented the state agency perspective on stem cell therapy for musculoskeletal conditions. Find the full presentation published with the [June 12, 2020, meeting materials](#).

Scheduled and open public comments: Chair called for public comments. Comments provided by:

- Leslie Emerick, Director, Public Policy, WA Acupuncture and Eastern Medicine Association

Vendor report/HTCC question and answers: Erika D. Brodt, BS, Aggregate Analytics, Inc., presented the evidence review for stem cell therapy for musculoskeletal conditions. Find the full report published with the [June 12, 2020, meeting materials](#).

Draft

HTCC coverage vote and formal action:***Committee decision***

Based on the deliberations of key health outcomes the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and state agency utilization information. The committee decided that the current evidence on stem cell therapy for musculoskeletal conditions is sufficient to make a determination on this topic. The committee discussed and voted on the evidence for the use of stem cell therapy for musculoskeletal conditions. The committee considered the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to not cover stem cell therapy for musculoskeletal conditions.

	Not covered	Covered under certain conditions	Covered unconditionally
Stem cell therapy for musculoskeletal conditions	10	0	0

Discussion

The committee reviewed and discussed the available studies for use of stem cell therapy for musculoskeletal conditions. Details of study design, inclusion criteria, outcomes and other factors affecting study quality were discussed. A clinical expert member provided detailed insight and discussion points. All committee members found the evidence sufficient to determine that use of stem cell therapy for musculoskeletal conditions is unproven for efficacy. A majority of committee members found the evidence sufficient to determine the use of stem cell therapy for musculoskeletal conditions is unproven for cost-effectiveness. Based on the evidence presented, all members of the committee found the use of stem cell therapy for musculoskeletal conditions to be either less safe than comparators, or unproven.

Limitations

N/A

Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). There is no Medicare national or local coverage determination for stem cell therapy for musculoskeletal conditions.

Five evidence based clinical guidelines and consensus statements were identified for this review. The committee discussed guidelines from the following organizations related to the use of stem cells for the treatment of musculoskeletal conditions:

- American Society of Interventional Pain Physicians (ASIPP), Responsible, Safe, and Effective Use of Biologics in the Management of Low Back Pain: ASIPP Guidelines, 2019
- International Society for Stem Cell Research (ISSCR), Current State of Cell-based Therapies for Osteoarthritis, 2019
- Australasian College of Sports Physicians (ACSP), ACSP—Position Statement: The Place of Mesenchymal Stem/Stromal Cell Therapies in Sport and Exercise Medicine, 2016

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- International Society for Stem Cell Research (ISSCR), Guidelines for Stem Cell Research and Clinical Translation, 2016
- American Academy of Orthopaedic Surgeons (AAOS), Optimizing Clinical Use of Biologics in Orthopaedic Surgery: Consensus Recommendations From the 2018 AAOS/NIH U-13 Conference, 2018

The committee's coverage determination is consistent with the identified guidelines.

The committee discussion included concerns published by the Food and Drug Administration (FDA), and detailed in the evidence report.

The committee chair directed HTA staff to prepare a findings and decision document on the use of stem cell therapy for musculoskeletal conditions for public comment to be followed by consideration for final approval at the next public meeting.

5. Meeting adjourned

**Health Technology Clinical Committee
DRAFT Findings and Decision**

Topic: Tinnitus: non-invasive, non-pharmacologic treatments
Meeting date: May 15, 2020
Final adoption: Pending

Meeting materials and transcript are available on the [HTA website](#).

Number and coverage topic:

20200515A – Tinnitus: non-invasive, non-pharmacologic treatments

HTCC coverage determination:

For adults with subjective tinnitus that is bothersome cognitive behavioral therapy is a **covered benefit**.

Sound therapies including masking devices are **not covered**.*

Repetitive transcranial magnetic stimulation is **not covered**.

HTCC reimbursement determination:

Limitations of coverage:

N/A

Non-covered indicators:

*Hearing aids for treatment of hearing loss are outside the scope of this determination.

Agency contact information:

Agency	Phone Number
Labor and Industries	1-800-547-8367
Public Employees Health Plan	1-800-200-1004
Washington State Medicaid	1-800-562-3022

Draft

HTCC coverage vote and formal action:

Committee decision

Based on the deliberations of key health outcomes the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and state agency utilization information. The committee decided that the current evidence on non-invasive, non-pharmacologic treatment of tinnitus is sufficient to make a determination on this topic. The committee discussed and voted on the evidence for the use of non-invasive, non-pharmacologic treatments for treatment of tinnitus. The committee considered the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to cover cognitive behavioral therapy for treatment of tinnitus. The committee voted to not cover sound therapies including masking devices, repetitive transcranial magnetic stimulation and tinnitus specific therapies for the treatment of tinnitus.

	Not covered	Covered under certain conditions	Covered unconditionally
Cognitive behavioral therapy	0	0	10
Sound therapies including masking devices	10	0	0
Repetitive transcranial magnetic stimulation	10	0	0
Tinnitus specific therapies	9	1	0

Discussion

The committee reviewed and discussed the available studies for use of non-invasive, non-pharmacologic therapies for treatment of tinnitus. Details of study design, inclusion criteria, outcomes and other factors affecting study quality were discussed. A clinical expert member provided detailed insight and discussion points. A majority of committee members found the evidence sufficient to determine that use of cognitive behavioral therapy for the treatment of tinnitus is safe and efficacious, but unproven for cost-effectiveness. The committee found the evidence is insufficient to make a conclusion about whether repetitive transcranial magnetic stimulation, sound therapies and tinnitus-specific therapies are safe, effective and cost-effective for the treatment of tinnitus.

Limitations

N/A

Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). There is no Medicare national or local coverage determination for the tinnitus treatments considered in this review..

Six evidence based clinical guidelines were identified for this review. The committee discussed guidelines from the following organizations related to the treatment of tinnitus:

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- National Institutes for Health and Care Excellence (NICE) Guideline: Tinnitus assessment and management, 2020
- A multidisciplinary European guideline for tinnitus: diagnostics, assessment, and treatment, 2019
- Association of the Scientific Medical Societies in Germany Guideline 01 7/064: Chronic Tinnitus, 2015
- American Academy of Otolaryngology-Head and Neck Surgery Clinical Practice Guideline: Tinnitus, 2014
- International Federation of Clinical Neurophysiology: Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation, 2014
- VA/DoD Clinical Practice Guidelines: Management of Concussion-mild Traumatic Brain Injury, 2016

The committee's coverage determination is consistent with the identified guidelines.

The committee chair directed HTA staff to prepare a findings and decision document on the use of non-invasive, non-pharmacologic treatments for tinnitus for public comment to be followed by consideration for final approval at the next public meeting.

Health Technology Clinical Committee Authority:

Washington State's legislature believes it is important to use a science-based, clinician-centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority (HCA), through its Health Technology Assessment (HTA) program, to engage in an evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company and that takes public input at all stages.

Pursuant to RCW 70.14.110 a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State HTCC determines how selected health technologies are covered by several state agencies (RCW 70.14.080-140). These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases its decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Director.

Draft

Tinnitus: non-invasive, non-pharmacologic treatments

Draft findings and decision
Timeline, overview and comments

The Health Technology Assessment (HTA) program received comments in response to the posted Health Technology Clinical Committee (HTCC) draft findings and decision on Tinnitus: non-invasive, non-pharmacologic treatments.

Timeline

Phase	Date	Public Comment Days
Technology recommendations published	March 13, 2019	
Public comments	March 13 to 27, 2019	15
Selected technologies published	April 1, 2019	
Public comments	April 1 to April 30, 2019	30
Draft key questions published	10/9/19	
Public comments	October 10 to October 23, 2019	14
Final key questions published	November 11, 2019	
Draft report published	February 26, 2020	
Public comments	February 27 to March 27, 2020	30
Final report published	April 14, 2020	
Public meeting	May 15, 2020	
Draft findings & decision published	May 19, 2020	
Public comments	May 19 to June 2, 2020	14
	Total	103

Overview

Category	Comment Period <i>May 19 to June 2, 2020</i>	Cited Evidence
Patient, relative, and citizen	0	0
Legislator and public official	1	0
Health care professional	0	0
Industry & manufacturer	0	0
Professional society & advocacy organization	0	0
Total	1	0

Comments

Respondents	Representing	Cited Evidence
<input type="checkbox"/> 1. Ian Zhao, PhD,	WA State Labor and Industries	

From: Zhao, Ian (LNI) <zhao235@LNI.WA.GOV>

Sent: Tuesday, July 7, 2020 9:34 AM

To: HCA ST Health Tech Assessment Prog <SHTAP@HCA.WA.GOV>

Cc: Franklin, Gary M. (LNI) <FRAL235@LNI.WA.GOV>; Fodeman, Jason D (LNI) <foja235@LNI.WA.GOV>; Daniel, Suzyn (LNI) <dsuz235@LNI.WA.GOV>

Subject: non-pharmacologic treatments for tinnitus

Dear HTCC,

I am commenting on behalf of L&I and would like to recommend the following clarifications to the determination language.

“Tinnitus specific therapy” or “Sound therapy” in the draft HTCC determination is not a term of art. It would be very helpful to define these terms clearly in the coverage language for proper implementation of the determination. It would be also helpful to include all the specific treatments reviewed by the committee.

Some sample language and proposed definitions are included for your reference:

- Tinnitus specific therapies* are not covered for the treatment of tinnitus, Including but not limited to:
 - o Tinnitus retraining therapy (TRT)
 - o Neuromonics tinnitus treatment (NTT)
 - o Tinnitus activities treatment (TAT)
 - o Tinnitus-masking counseling

- Sound therapies# are not covered for the treatment of tinnitus, including but not limited to:
 - o Masking devices (sound maskers)
 - o Hearing aids with sound-generating features
 - o Altered auditory stimuli
 - o Auditory attention training

- *Tinnitus-specific therapies refer to a group of interventions that combine components of sound therapy and counseling for the treatment of tinnitus. These include tinnitus retraining therapy, Neuromonics tinnitus treatment, tinnitus activities treatment, tinnitus-masking counseling, and others.

- #Sound therapy for tinnitus is broadly described as the use of sound to alter a patient’s perception of and reaction to tinnitus. This category includes sound maskers, altered auditory stimuli (e.g., listening to frequency-altered music), and hearing aids that may incorporate sound-masking features.

Thank you for your consideration.

Ian Zhao, Ph.D.

Washington State Dept. of Labor & industries

(360) 902-5026

Zhao235@lni.wa.gov

Tinnitus: non-invasive, non-pharmacologic treatments

HTCC final approval of coverage decision

(From page 7 of decision aid)

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 unclear outcome (i.e., tie), chair will lead discussion to determine next steps.

**Health Technology Clinical Committee
DRAFT Findings and Decision**

Topic: Vagal nerve stimulation for epilepsy and depression
Meeting Date: May 15, 2020
Final Adoption: Pending

Meeting materials and transcript are available on the [HTA website](#).

Number and coverage topic:

20200515B – Vagal nerve stimulation for epilepsy and depression

HTCC coverage determination:

Vagal nerve stimulation for epilepsy is a **covered benefit with conditions** consistent with the criteria identified in the reimbursement determination.

Vagal nerve stimulation for treatment-resistant depression is **not a covered benefit**.

Transcutaneous vagal nerve stimulation for epilepsy or depression is **not a covered benefit**.

HTCC reimbursement determination:

Limitations of coverage:

Vagal nerve stimulation for epilepsy is covered for adults and children (age 4 and older) when all of the following conditions are met:

- Seizure disorder is refractory to medical treatment, defined as adequate trials of at least 3 appropriate but different anti-epileptic medications.
- Surgical treatment is not recommended or has failed.

Non-covered indicators:

- Vagal nerve stimulation for the treatment of depression
- Transcutaneous vagal nerve stimulation

Agency contact information:

Agency	Phone Number
Labor and Industries	1-800-547-8367
Public Employees Health Plan	1-800-200-1004
Washington State Medicaid	1-800-562-3022

Draft

HTCC coverage vote and formal action:***Committee decision***

Based on the deliberations of key health outcomes the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and state agency utilization information. The committee decided that the current evidence on vagal nerve stimulation for epilepsy and depression is sufficient to make a determination on this topic. The committee discussed and voted on the evidence for the use of vagal nerve stimulation for the treatment of epilepsy and depression. The committee considered the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to cover with conditions vagal nerve stimulation for the treatment of epilepsy. The committee voted to not cover vagal nerve stimulation treatment of depression, and to not cover transcutaneous vagal nerve stimulation for epilepsy or depression.

	Not covered	Covered under certain conditions	Covered unconditionally
Vagal nerve stimulation for epilepsy	0	10	0
Vagal nerve stimulation for depression	7	3	0
Transcutaneous vagal nerve stimulation	10	0	0

Discussion

The committee reviewed and discussed the available studies for use of vagal nerve stimulation for treatment of epilepsy and depression. Details of study design, inclusion criteria, outcomes and other factors affecting study quality were discussed. A clinical expert member provided detailed insight and discussion points.

A majority of committee members found the evidence sufficient to determine that use of vagal nerve stimulation for the treatment of epilepsy in adults and children is safe and efficacious, but unproven for cost-effectiveness. All committee members found vagal nerve stimulation for epilepsy to be more effective in at least some cases, than comparators.

For treatment of depression the committee discussed details of the available clinical trial data. Half of the committee found the evidence insufficient to conclude the treatment to be safe, while the other half of the committee was split between concluding the evidence demonstrated it to be less safe or safer in some, than comparators. The majority of the committee found the evidence to be insufficient to make a conclusion related to effectiveness, and all committee members found insufficient evidence related to cost-effectiveness.

The committee unanimously found the evidence to be insufficient to conclude whether transcranial vagal nerve stimulation is safe, efficacious or cost-effective.

Limitations

N/A

Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). There is one Medicare national coverage decision on the use of VNS. The committee also reviewed the new criteria for the NCD under development for VNS in depression. The committee determination is not consistent with the Medicare determination of coverage for depression only if in a clinical trial based on the committee's consideration of the most recent evidence. The committee acknowledged the state programs may consider coverage for individuals when in the context of a clinical trial.

Six evidence based clinical guidelines related to VNS or tVNS for epilepsy were identified for this review. The committee discussed guidelines from the following organizations related to the treatment of epilepsy:

- National Institutes for Health and Care Excellence (NICE) Guideline: Epilepsies: diagnosis and management, 2012
- Scottish Intercollegiate Guidelines Network (SIGN), diagnosis and management of epilepsy in adults, 2015
- Task Force Report for the ILAE Commission of Pediatrics, Management of Infantile Seizures, 2015
- Australian Government Medical Services Advisory Committee (MSAC), VNS for refractory epilepsy, 2016
- Epilepsy Implementation Task Force, management of medically- refractory epilepsy in adults and children who are not candidates for epilepsy surgery, 2016
- Wirrel et al. on behalf of a North American Consensus Panel, Diagnosis and management of Dravet syndrome, 2017

Five evidence based clinical guidelines related to VNS or tVNS for depression were identified for this review. The committee discussed guidelines from the following organizations related to the treatment of depression:

- Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, management of depression in adults, 2014
- Canadian Network for Mood and Anxiety Treatments, neurostimulation in the management of major depressive disorder in adults, 2016
- Department of Veterans Affairs, Department of Defense, management of major depressive disorder, 2016
- Royal Australian and New Zealand College of Psychiatrists, Management of mood disorders, 2015
- Australian Government Medical Services Advisory Committee (MSAC), VNS for chronic major depressive episodes, 2018

The committee's coverage determination is consistent with the identified guidelines.

The committee chair directed HTA staff to prepare a findings and decision document on the use of vagal nerve stimulation for epilepsy and depression for public comment to be followed by consideration for final approval at the next public meeting.

Health Technology Clinical Committee Authority:

Washington State's legislature believes it is important to use a science-based, clinician-centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority (HCA), through its Health Technology Assessment (HTA) program, to engage in an evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company and that takes public input at all stages.

Pursuant to RCW 70.14.110 a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State HTCC determines how selected health technologies are covered by several state agencies (RCW 70.14.080-140). These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases its decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Director.

Draft

Vagal nerve stimulation for epilepsy and depression

Draft findings and decision
Timeline, overview and comments

The Health Technology Assessment (HTA) program received comments in response to the posted Health Technology Clinical Committee (HTCC) draft findings and decision on vagal nerve stimulation for epilepsy and depression.

Timeline

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Overview

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Patient, relative, and citizen	0	0
Legislator and public official	0	0
Health care professional	0	0
Industry & manufacturer	1	1
Professional society & advocacy organization	1	0
Total	2	1

Comments

Respondents			Cited Evidence
<input type="checkbox"/>	1. David Dunner, MD	Center for Anxiety and Depression	No
<input type="checkbox"/>	2. Eliza Hagen, MD, MBA Ryan Verner, PhD	LivaNova	Yes



June 15, 2020

TO: shtap@hca.wa.gov

RE: WA HCA Draft findings and decision regarding Vagus Nerve Stimulation therapy for Depression

I thank you for allowing me to make a brief presentation at the meeting and to listen to the proceedings. I understand the lack of another sham controlled trial of VNS for treatment of individuals with treatment resistant depression presented somewhat of stumbling block for the committee, even though this treatment is FDA approved for this indication.

I wish to make two additional comments: First, it is disappointing that there was no psychiatrist, let alone a psychiatrist familiar with depression or treatment resistant depression, on the committee. The committee included membership from a child neurologist to address concerns regarding VNS for children with epilepsy but did not consider an inside perspective from a psychiatrist.

Second, "a majority of the committee members found the evidence sufficient to determine that use of vagal nerve stimulation for the treatment of epilepsy in adults and children is safe and efficacious..." and also, for the treatment of depression, "Half of the committee found the evidence insufficient to conclude the treatment to be safe, while the other half of the committee was split between concluding the evidence demonstrated it to be less safe or safer in some, than comparators." I am not aware of the evidence that the committee used to determine that a device is safer in a population with one disorder compared with patients who have a different disorder. Perhaps the committee would be kind enough to share this evidence with me so I can better inform my patients of the unique risks that having depression imparts on the safety of a device.

Sincerely yours,

David L Dunner, MD, FACPsych

Director, Center for Anxiety and Depression

June 18, 2020

Via Email: shtap@hca.wa.gov

Dear Washington Healthcare Authority Clinical Committee:

On behalf of LivaNova, we would like to provide the Committee with additional comments regarding the Health Technology Clinical Committee's draft Findings and Decision on Vagal Nerve Stimulation for epilepsy and depression. We would like to thank you for the opportunity to participate in the discussion and provide limited input during the meeting. Unfortunately, due to some technical difficulties, some of the information we wanted to provide or clarify during the meeting was not received. We believe that had the meeting been in person, some of this information would have been available to the committee and might have changed the outcome of the draft findings. For these reasons, we respectfully submit the following comments for your consideration.

Epilepsy

We appreciate that the Committee voted to approve vagal nerve stimulation for epilepsy; however, we are concerned with the conditions of coverage that are outlined in the draft. Under the limitations of coverage, the Committee has defined seizure disorder as refractive to medical treatment if there has been an adequate trial of at least 3 appropriate but different anti-epileptic medications. During the May meeting the ILAE guideline was referenced as using this guideline. Attached for your consideration and review are two peer reviewed papers and one specialty society guideline supporting trials of 2 or more different anti-epileptic medications.

- Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies
- A validation of the new definition of drug-resistant epilepsy by the International League Against Epilepsy
- Quality improvement in neurology: Epilepsy Update Quality Measurement Set by the American Academy of Neurology (AAN), 2015.

These two papers along with the AAN Guidelines, discuss seizure disorder that is refractory to medical treatment; defined as adequate trials of at least 2 appropriate but different anti-epileptic medications.

In addition, no other payer coverage policy requires a failure of at least 3 appropriate but different anti-epileptic medications. This requirement would cause further delay for a patient to access needed therapy. It is well documented in peer reviewed literature that prolonged, uncontrolled epilepsy results in worsening cognitive outcomes (particularly in children) and an increase in depressive behavior, suicidal mortality, incidence of status epilepticus episodes and SUDEP, sudden cardiac death, and death due to traffic accidents, drowning, or other injuries (Stelzer FG et al. *Arq Neuropsychiatr* 2015;73(8):670-675.; Neligan A et al. *Brain* 2011: 134: 388–395; Mohanraj R et al, *Lancet Neurol* 2006; 5: 481–877; Tian N et al *Epilepsy & Behavior* 2016: 61: 210-217; Garcia ME et al *Epilepsy Research* 2015; 110: 157—165; Helmstaedter C, Witt JA. *Seizure* 2017; 49: 83–89,).

Depression

We understand that the Committee voted to not cover VNS for depression under any conditions. LivaNova believes a major contributing factor to that decision was a lack of psychiatric clinical expert input and understanding of this severely ill patient population. If you were to stage depression as if it were cancer, these patients would most often be stage 4. Put into that context, we offer the following comments for your review and consideration.

Lack of clinical expert in depression at May 15 meeting

According to the HCA website, beginning in November 2016, appointed, non-voting clinical experts may be asked to join the Committee in review of a specific technology. We appreciate that the Committee had an epileptologist available for the discussion on epilepsy but we are disappointed that the Committee did not have any external or internal clinical expertise on depression. While there were several public comments made during the meeting, 3 minutes is not enough time to make any substantive points on this very complex patient population. In addition, the draft report states that a clinical expert member provided detailed insight and discussion points. We do not believe this to be an accurate statement as it relates to the discussion on depression due to the absence of an expert in depression. In the future, we encourage the Committee to reach out to the WA Chapter of the American Psychological Association (WA APA) to request a clinical expert in depression.

Clinical patient profile

In the limited amount of time provided them during the May 15th meeting, Doctors Allen, Dunner and Gwinn provided a description of the appropriate VNS candidate and where VNS fits in the treatment algorithm. They described patients who experience an unremitting chronic episode of MDD and/or experience initial recovery with later recurrence of depressive illness causing prolonged suffering, negative health outcomes and who are at a greater risk of suicide than their remitted counterparts. These patients have already tried numerous antidepressant treatments including pharmacotherapy, psychotherapy, and unsuccessful courses of rTMS and/or ECT and yet, their severe symptoms persist, are frequently debilitating and negatively affect their quality of life.

VNS Therapy for depression is not a front-line treatment. It is a treatment option for the small subset of patients who, at this stage in their disease, lack other options for an effective and durable treatment of this more difficult to treat form of major depressive disorder. As outlined by the key opinion leaders, VNS Therapy offers these patients the best chance for improving their severe depressive symptoms and the potential benefits far outweigh the potential risks (including risk of suicide) of continuing ineffective treatment as usual.

These key opinion leaders placed VNS in the same position in the treatment pathway as the American Psychiatric Association's (APA) 2010 Practice Guidelines for the Treatment of Major Depressive Disorder. The American Psychiatric Association (APA) is the main [professional organization](#) of [psychiatrists](#) and trainee psychiatrists in the [United States](#), and the largest [psychiatric](#) organization in the world.^[4] Its some 38,800^[4] members are mainly American but some are international. As the leading professional organization in the United States for Psychiatry, we believe the 2010 Practice Guideline for the

Treatment of Patients with Major Depressive Disorder, Third Edition was submitted by LivaNova previously and should have been considered.

In the guidelines, the APA provides clear guidance related to where in the treatment pathway a psychiatrist should consider treatment with VNS. Page 15 specifically indicates that VNS, “may be recommended on the basis of individual circumstances”, clearly indicating VNS may be used when medically necessary. Furthermore, page 19 states, “VNS may be an additional option for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT.” The guidelines address the durability of VNS therapy on p. 46, saying, “Vagus nerve stimulation therapy is approved for use based on potential long-term treatment benefits.” Lastly, p. 56 of the guidelines state that while VNS is not an acute treatment for depression, “persistent benefits...could be clinically significant for some patients.”

Poorly understood mechanism of action

During the meeting on May 15, a comment was made that the mechanism of action of VNS Therapy is poorly understood. We would like to offer additional educational information as to the evidence available on the VNS Therapy mechanism of action in depression.

A number of studies have been published that characterize the mechanism of action of VNS therapy in terms of both the effect areas of the brain and subsequent changes in neurotransmitters, specifically serotonin, norepinephrine, gamma-aminobutyric acid and aspartate.

Brain imaging studies have demonstrated that sustained treatment with VNS Therapy acts upon several regions of the brain known to be critical in mood regulation.

In a National Institute of Mental Health (NIMH) sponsored brain imaging trial, using ¹⁸Fluorodeoxyglucose positron emission tomography (FDG-PET) and resting state cerebral metabolic regional glucose uptake (CMRGl_u), Conway et al. (2013)¹ serially imaged 13 patients with TRD at baseline (post-implantation, pre-stimulation) and after 3 and 12 months of VNS stimulation. The patient population was highly treatment-resistant (patients failed to respond to an average of ≥ 7 antidepressants), 69% had prior ECT therapy, and experienced an average of over 2 psychiatric hospitalizations. Consistent with epidemiology studies, patients were, on average, 46 years old, 77% were female and had an average early age of onset of 19 years old.

The majority of TRD patients (9/13) in this study responded (decreased baseline depression score by $\geq 50\%$) to 12 months of stimulation. A within-subjects (responders-only), regions-of-interest design was used to assess changes in CMRGl_u. Key findings of this study were as follows:

- Statistically significant decreases were observed in mean regional CMRGl_u in the right dorsolateral prefrontal cortex (DLPFC; Brodmann’s area 46) after three months of stimulation in patients whose depressive symptoms eventually (12 months) responded to VNS Therapy.

¹ Conway CR, Chibnall JT, Gebara MA, Price JL, Snyder AZ, Mintun MA, Craig AD, Cornell ME, Perantie DC, Giuffra LA, Bucholz RD, Sheline YI. Association of cerebral metabolic activity changes with vagus nerve stimulation antidepressant response in treatment-resistant depression. *Brain Stimulation*, 2013;6(5):788-97. PMID: PMC3954813.(Attachment 12)

- In contrast, no DLPFC changes were seen in those 4 patients with TRD who failed to respond to 12 months of VNS Therapy.
- CMRGlu decreases (not statistically significant) were noted at 3 months in the right anterior insular and cingulate cortices, also regions known to be critical in depression².
- Increased regional CMRGlu was noted in the left substantia nigra/ventral tegmental area (VTA) brainstem region at 12 months in all 9 responders, while the opposite pattern (VTA decrease in regional CMRGlu) was noted in non-responders.

These results are important in confirming the antidepressant role of VNS Therapy given that:

- Brodmann's area 46 is a region well-known to be critical in depression³; and
- The VTA is the primary brainstem region modulating dopamine, a neurotransmitter thought to be potentially critical in major depressive disorder and TRD⁴. The 12 month findings may suggest VNS Therapy acts in TRD by activation of dysfunctional brainstem dopaminergic loci. This is further substantiated by research⁵ which demonstrated active VNS Therapy (but not sham VNS) in TRD brought about increased cerebrospinal fluid concentrations of homovanillic acid, the primary metabolite of dopamine.

A second NIMH-sponsored study⁶ assessed whether baseline regional cerebral metabolic activity correlated with eventual antidepressant outcome using FDG-PET and a regions-of-interest regression analysis. Key findings of this study included:

- The lower anterior insular cortex CMRGlu ($p = 0.004$) and higher orbitofrontal cortex CMRGlu ($p = 0.047$), both regions known to be critical in depression⁷ jointly predicted change in the 24 item Hamilton Depression Rating Scale (HDRS) ($R^2 = 0.58$, $p = 0.005$).
- In a whole brain, voxel-wise analysis, baseline CMRGlu in the right anterior insular cortex correlated with HDRS change ($r = 0.78$, $p = 0.001$).

These findings suggest that baseline anterior insular and orbitofrontal cortex metabolic activity may influence antidepressant outcomes at 12 months.

Neurotransmitter system studies

While it is clinically difficult to measure changes in the neurotransmitter system within the brain, a number of studies have provided evidence that treatment with VNS Therapy has a positive effect on those neurotransmitters known to affect mood.

² Price JL, Drevets WC. Neurocircuitry of Mood Disorders. *Neuropsychopharmacology*. 2010;35(1):192–216.

³ Price, et al. op. cit.

⁴ Nestler EJ, Carlezon Jr. WA. The Mesolimbic Dopamine Reward Circuit in Depression. *Biol Psychiatry*, 2006; 59(12):1151-1159.

⁵ Carpenter LL, Moreno FA, Kling MA. Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients. *Biol Psychiatry*, 2006;56(6):418-426.

⁶ Conway CR, Chibnall JT, Gangwani S, Mintun MA, Price JL, Hershey T, Giuffra LA, Bucholz RD, Christensen JJ, Sheline YI. Pretreatment cerebral metabolic activity correlates with antidepressant efficacy of vagus nerve stimulation in treatment-resistant major depression: A potential marker for response? *J Aff Disorders*, 2012;139(3):283-290 PMID: PMC3598572.

⁷ Price, et al. op. cit.

In one study ^{REF1}, conducted by the Neurology Service at the West Los Angeles VA, in rats that were chronically depleted of norepinephrine (NE) the application of Vagus Nerve Stimulation was found to activate the locus coeruleus (LC) and result in increased levels in the brain.

In a second study ^{Ref 2} 10 patients received high and low levels of stimulation and, after 3 months, had cerebrospinal fluid (CSF) collected. All patients who responded to VNS therapy showed significantly increased levels of total and free gamma-aminobutyric acid (GABA) levels.

In a third study conducted by Hammond et al at the Veterans Affairs Medical Center in Gainesville FL the CSF of 6 patients with partial seizures were studied before and after VNS therapy. The study found that 5-hydroxyindoleacetic acid (5-H1AA) and homovanillic acid (HVA) both significantly increased. Both 5-H1AA and HVA are metabolites of neurotransmitters Serotonin and Dopamine respectively. Additionally, the study showed a decrease in levels of Aspartate.

In summary, there has been significant progress in understanding the mechanism of action of VNS Therapy in TRD and it is imperative that we share this with the committee due to the misleading statement regarding mechanism of action. This work continues to demonstrate that VNS Therapy acts by changing activity in brain regions known to be critical in depression (pre-frontal and insular cortex, dorsolateral prefrontal regions, anterior cingulate cortex, as well as brainstem mesolimbic regions).

Confusion around Dr. Aaronson publications

Dr. Aaronson is the lead author on several papers related to VNS for treatment resistant depression. During the meeting on May 15, there was discussion surrounding the inclusion of the 5-year outcomes from the 2017 paper which was published in the American Journal of Psychiatry. The initial draft of the HTA did not include the 2017 publication and LivaNova submitted it as part of our comments. However, according to the list of papers excluded from the final report, *A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality* remained on the list of excluded studies. We respectfully request that the committee review the results of this study which demonstrated significant and sustained benefit with adjunctive VNS Therapy relative to patients treated with treatment-as-usual over a 5- year follow-up.

Study design: Multicenter, prospective, open-label, nonrandomized, observational registry study in which 795 patients with TRD were treated: 494 with adjunctive VNS therapy and 301 with treatment-as-usual.

Study duration: Patients were followed for 5 years.

Patient Population: The patient population was highly treatment-resistant (patients failed to respond to an average of ≥ 7 previous treatments), over 50% had prior ECT therapy, averaged between 1 and 2 prior suicide attempts and 2-3 psychiatric hospitalizations over the past 5 years. Consistent with epidemiology studies, patients were on average 49 years old and 70% were female.

Results: The registry results indicate that the adjunctive VNS group had better clinical outcomes than the treatment-as-usual group, including a significantly higher 5-year cumulative response rate

(67.6% compared with 40.9%) and a significantly higher remission rate (cumulative first-time remitters, 43.3% compared with 25.7%). A sub-analysis demonstrated that among patients with a history of response to ECT, those in the adjunctive VNS group had a significantly higher 5-year cumulative response rate than those in the treatment-as-usual group (71.3% compared with 56.9%). A similar significant response differential was observed among ECT non-responders (59.6% compared with 34.1%).

Conclusions: This registry represents the longest and largest naturalistic study of efficacy outcomes in treatment-resistant depression, and it provides additional evidence that adjunctive VNS has enhanced antidepressant effects compared with treatment as usual in this severely ill patient population.

Medicare Coverage of VNS for TRD

As discussed in our previous comment letters, Medicare is covering VNS for depression under the Coverage with Evidence (CED) program. In addition, outside of a clinical trial Medicare is covering battery replacements for patients that have previously been implanted with the device and need to have the battery changed in order to continue receiving therapy. CMS has just released an updated MedLearn Matters article (attached) and an update to the CMS NCD coverage manual (attached). LivaNova understands that WA HCA is not required to follow Medicare coverage guidelines; however we would like to request coverage of battery replacements. Failure to allow for battery replacements may result in patients who have experienced a reduction in or remittance of their depressive symptoms with subsequent improvement in their quality of life returning to depressive symptoms when the battery is depleted.. Without an explicit coverage policy, these patients will be put at risk for a return to depressive symptoms and an increase in suicidality.

Treatment Resistant Bipolar Disorder

The Committee failed to recognize that 'Treatment Resistant Depression' (TRD) patients are not a homogeneous patient population and in fact have different clinical challenges and different therapeutic options available to them. Patients who present with a diagnosis of 'Treatment Resistant Bipolar Depression' (TRBPD) are symptomatic about 50% of the time, the vast majority of which is spent in the depressive episode.

However, unlike TRD patients, TRBPD patients have a limited treatment options available to them. For example, the UK National Institute for Health and Care Excellence, list just 3 treatments that are supported by solid evidence; lamotrigine, quetiapine and olanzapine. This small list is further compromised as both quetiapine and olanzapine are often poorly tolerated due to weight gain and sedation.

Non drug options for TRBPD patients are also very limited, with only VNS and ECT indicated for use in TRBPD patients.

Further evidence ^{REF 4} of the efficacy and safety of VNS therapy in TRBPD was recently published in the International Journal of Bipolar Disorders. This 5 year, real world evidence trial, showed that when VNS

therapy is added to treatment as usual (VNS +TAU) vs treatment as usual (TAU) alone, 63% of patients had a response for VNS + TAU compared with 39% for TAU and further the mean reduction in suicidality score was significantly greater for VNS+TAU group than TAU alone.

Unlike VNS, which is indicated for adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older and are experiencing a major depressive episode and have not had an adequate response to 4 or more antidepressant treatments, TMS has not been approved for use in Bipolar patients. In fact, there is a specific warning against the use of TMS in this patient population.

Denying TRBPD patients access to VNS therapy, an FDA approved treatment that is proven to be effective and safe, leaves patients with the option of ECT or nothing. In the best interests of patients we strongly urge WA to reconsider the decision for this patient population.

Coverage of TMS

Towards the end of the meeting, one committee member made a statement that TMS should be covered not realizing that it was already covered by the WA HCA. It should be noted that like VNS for depression, TMS is indicated for use in the treatment of Major Depressive Disorder in adult patients who have failed to receive satisfactory improvement from prior antidepressant medication in the current episode. VNS which is indicated for ***adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments.*** TMS is typically used early in the treatment pathway but it is not indicated for treating patients with bipolar depression. This is significant because VNS for Depression has been studied in bipolar patients and is not off-label. For patients that are diagnosed as bi-polar, outside of medications and ECT, without coverage of VNS, these patients have no other options.

Risk vs Benefit of VNS Therapy

VNS therapy was characterized, by some members of the panel as a 'risky intervention'. LivaNova would like to take the opportunity to remind the panel that the risks and benefits of VNS therapy have been fully evaluated by the FDA who have approved for use in the indicated population as stated above. Since FDA approval, across multiple diseases and over 25 years, over 100,000 patients have been implanted with VNS therapy and we have over 1 million patient years of experience.

VNS therapy is not burdened with the side effects of pharmacological therapies such as weight gain, somnolence, blurred vision, etc. VNS therapy does not have the side effects that limit the repeated use of ECT such as cognitive decline. The most common side effects of VNS therapy, in clinical trials, were stimulation related (voice alteration, cough, dyspnea) and implant related (incision pain, voice alteration, incision site reaction). Despite these, when added to conventional therapy, VNS therapy does not impart a clinically greater side effect burden than that seen with conventional treatment alone. Furthermore, the side effects related to stimulation are well tolerated and tend to diminish over time.

Against this background of 'risk' VNS therapy in long term clinical trials has demonstrated a 'benefit' of; a significantly higher 68% cumulative response rate, a significantly higher 43% cumulative remission rate, a decrease of 50% in rate of suicide and a 2X decrease in suicidality compared to treatment as usual.

TRD is a deadly illness (an estimated 15% die by suicide) and recent evidence from the Centers for Disease Control and Prevention (CDC)⁸ shows rates of suicide have increased by 24% over the past decade. Similarly, recent studies demonstrate that, on average, a U.S. Veteran dies by suicide every hour⁹.

Carefully designed, prospective studies, such as the large, multicenter VNS Therapy studies described in this request (D-21 Dosing Study and D-23 TRD Registry) that studied patients with TRD having well-documented treatment failure (with adequate dose and duration) histories should be sufficient to reconsider coverage of VNS Therapy for TRD.

These patients are in desperate need of treatment options and we believe that the weight of scientific evidence provided in the HTA and this request for reconsideration supports coverage of VNS Therapy as a treatment option.

On behalf of this underserved and vulnerable patient population, the physicians who provide care for them and LivaNova, we would like to request reconsideration of coverage for VNS for depression to be reclassified as coverage with conditions. We propose the Clinical Committee consider limited coverage for VNS for depression for patients that:

- Are at least 18 years of age or older.
- Have a documented diagnosis of chronic (≥ 2 years) or recurrent (4 or more prior episodes, separated by two months without meeting criteria for MDD) major depressive disorder, according to DSM 5 criteria,
- Has unable to achieve remission and/or maintain durability of treatment effect despite treatment with at least four appropriate and adequate antidepressant treatments, including multiple medications / psychotherapy / ECT / rTMS
- Must have tried rTMS and/or ECT unless there is a valid reason the psychiatrist does not or no longer recommends, or the patient refuses these therapies.

Another option would be for the Clinical Committee to provide coverage for VNS for depression to bipolar patients that:

- Are at least 18 years of age or older
- Have a documented diagnosis of chronic (≥ 2 years) or recurrent (4 or more prior episodes, separated by two months without meeting criteria for MDD) major depressive disorder, according to DSM 5 criteria,
- Has unable to achieve remission and/or maintain durability of treatment effect despite treatment with at least four appropriate and adequate antidepressant treatments, including multiple medications / psychotherapy / ECT
- Must have tried ECT unless there is a valid reason the psychiatrist does not or no longer recommends, or the patient refuses these therapies.

⁸ Curtin SC, Warner M, Hedegaard H. Increase in suicide in the United States, 1999–2014. NCHS data brief, no 241. Hyattsville, MD: National Center for Health Statistics. 2016. (Attachment 17)

⁹ Kemp J, Bossarte R. Suicide Data Report, 2012. Department of Veterans Affairs Mental Health Services Suicide Prevention Program. <https://www.va.gov/opa/docs/suicide-data-report-2012-final.pdf>. (Attachment 18)

Thank you for your consideration of this formal request for reconsideration of the limitations of coverage for epilepsy and the non-coverage of VNS for depression. We appreciate the opportunity to participate in the process.

Sincerely,



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Enclosed:

Aaronson et al 2017
Aaronson et al 2017 supplemental materials
APA 2010 Major Depressive Disorder Guidelines
MedLearn Matters
CMS NCD Coverage Manual Update

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Quality improvement in neurology

Epilepsy Update Quality Measurement Set



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Epilepsy is a common, debilitating, and costly disease. It is estimated that 2.2 million people in the United States are diagnosed with epilepsy, and 150,000 new cases of epilepsy are diagnosed in the United States annually.¹ However, epilepsy prevalence might be underestimated due to numerous social issues that accompany a diagnosis of epilepsy.² People with epilepsy have poorer overall health status, impaired intellectual and physical functioning, and a greater risk for accidents and injuries.¹⁻³ It is estimated that the annual direct medical cost of epilepsy in the United States is \$9.6 billion, and this estimate does not include indirect costs from losses in quality of life or productivity.¹

In 2013, the American Academy of Neurology (AAN) formed a multidisciplinary Epilepsy Update Quality Measurement Set workgroup to review the previously released quality measures, as well as to identify and define new quality measures aimed at improving the delivery of care and outcomes for patients with epilepsy.⁴ The first AAN Epilepsy Quality Measures were approved by a similar process in 2009, and as part of the AAN's measure development process undergo a periodic review. During each periodic review, the evidence base is reviewed to determine if existing measures continue to be supported by the evidence, continue to address a treatment gap, or require updates to address new developments in these areas. In this executive summary, we report on the 2014 updated quality measurement set for epilepsy developed by the workgroup (table 1). The full measurement set, including specifications, is available in appendix e 1 on the *Neurology*® Web site at Neurology.org.

The AAN, which has designed and coordinated several quality measurement sets, including for Parkinson disease, dementia, and amyotrophic lateral sclerosis, led this measure development project.⁵⁻⁷ The details of the full AAN measurement development process are available online.⁸ The AAN Epilepsy Update Quality Measurement Set includes measures that can be used in quality improvement initiatives, public reporting, payment, and Maintenance of Certification (MOC) performance in practice programs. Three 2009 epilepsy measures were adopted into pay for performance programs.

OPPORTUNITIES FOR IMPROVEMENT Quality epilepsy care includes proper diagnosis, patient and family education, timely referrals, and access to treatment.¹ A review of 261 patient responses using an Internet based patient survey system indicated that a gap remains between recommended care detailed in the 2009 epilepsy measurement set and the care delivered to patients with epilepsy.⁹

Diagnosis. Providers often fail to gather information on seizure frequency effectively.^{4,9,10} In addition, there is a gap in known seizure etiology.^{4,10-13} According to the International League Against Epilepsy (ILAE), the treatment for differing kinds of epilepsy varies; a treatment for one can be specifically contraindicated in another.¹⁴ This strongly suggests that a clear understanding of each patient's diagnosis by the practitioner would improve patient care.

Education. Research indicates that people with epilepsy frequently misunderstand basic information about epilepsy, including knowledge about their

Supplemental data
at Neurology.org

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Approved by the AAN Quality and Safety Subcommittee on July 3, 2014; by the AAN Practice Committee on July 18, 2014; and by the AANI Board of Directors on August 6, 2014.

This measurement set was endorsed by the Child Neurology Society on July 29, 2014, and the Epilepsy Foundation on August 7, 2014. This measurement set received a qualified endorsement by the American Epilepsy Society (AES) on July 29, 2013. AES definition of qualified endorsement: Quality measurement sets developed by external organizations that may not meet optimal levels of evidence and/or may not provide complete clinical decision support will be considered for qualified endorsement. The AES may not agree with every recommendation in such a document but overall considers the information to be of educational value to its members and to provide the basis for further analysis and validated measure development.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Table 1 2014 Epilepsy Update Quality Measurement Set

1A. Seizure frequency specified at each encounter (paired measure) (2009 measure revised)
1B. Seizure intervention specified at each encounter (paired measure) (2009 measure revised)
2. Etiology, seizure type, and epilepsy syndrome specified at each encounter (2009 measure revised)
3. Querying and intervention for side effects of antiseizure therapy specified at each encounter (2009 measure revised)
4. Personalized epilepsy safety issue and education provided yearly (2009 measure revised)
5. Screening for psychiatric or behavioral health disorders specified at each encounter (new measure)
6. Counseling for women of childbearing potential with epilepsy yearly (2009 measure affirmed with updated specifications)
7. Referral of treatment resistant epilepsy to comprehensive epilepsy center every 2 years (new measure)

diagnosis, seizure precipitants or triggers, specific seizure types, the purpose and potential side effects of seizure medications and therapies, safety concerns, and the risks of seizures.^{1,4,15 18} Data from measure testing showed that on average, fewer than 40% of women received counseling about epilepsy and how its treatment may affect contraception and pregnancy.¹⁹ An AAN evidence based guideline provides recommendations for counseling on these issues.²⁰ People with epilepsy, their families, and their caregivers want more information than they currently receive, and this includes information on sudden unexplained death in epilepsy.^{1,21} Education should be provided in the best manner to meet their specific situations, as patients may not request this information because they are embarrassed or intimidated.

Timely referrals and access to treatment. Evidence indicates that the chance of seizure freedom is substantially reduced after failure of an adequate trial of the first 2 antiseizure medications. This mirrors the ILAE definition, which defines pharmaco-resistant epilepsy as failure of adequate trials of 2 tolerated, appropriately chosen and used antiepileptic drugs (whether as monotherapy or in combination) to achieve sustained seizure freedom.^{22,23} Evidence suggests that surgery increases seizure freedom rates often in excess

Table 2 2009 Epilepsy measurement set

1. Seizure type(s) and current seizure frequency(ies)
2. Documentation of etiology of epilepsy or epilepsy syndrome
3. EEG results reviewed, requested, or test ordered
4. MRI/CT scan results reviewed, requested, or scan ordered
5. Querying and counseling about antiepileptic drug side effects
6. Surgical therapy referral consideration for intractable epilepsy
7. Counseling about epilepsy specific safety issues
8. Counseling for women of childbearing potential with epilepsy

of 50%, and seizure freedom is related to improved quality of life.^{24,25} The time to referral to epilepsy surgery centers is frequently over 20 years despite evidence of high seizure freedom rates following epilepsy surgery and an AAN evidence based guideline addressing referral for epilepsy surgery.^{26,27} Many practitioners may not recognize a patient is a surgical candidate for epilepsy. However, referral to a comprehensive multidisciplinary epilepsy center ensures that all potential diagnostic and treatment options are considered and comorbidities are addressed, thus improving the quality of care that patients with epilepsy receive.

METHODS The AAN epilepsy update quality measurement development process followed the same AAN process used to develop the original epilepsy measures.^{4,8} The steps in the measure development process require completing an evidence-based literature search, constructing draft measures and technical specifications, and convening a multidisciplinary workgroup, which was composed of representatives from 17 different professional and patient advocacy organizations to review draft candidate measures. The workgroup met via conference calls and correspondence and convened for a full-day in-person meeting for a robust discussion of the candidate measures. Public comments were solicited during a 30-day period, which included notifications through the organizations represented in the workgroup. The measures and corresponding technical specifications were refined, and approvals obtained from the workgroup, AAN committees, and the AAN Board of Directors.⁸ The workgroup sought to develop measures to support the delivery of high-quality care and to improve patient outcomes. The AAN will continue to update the epilepsy measures on an ongoing basis every 3 years.

RESULTS Epilepsy Update Quality Measurement Set. The workgroup reviewed the original 8 measures developed in 2008 2009 during a face to face meeting on January 23, 2014⁴ (table 2). Appendix e 1 lists the final full measure set with rationale and reasons why a patient may be excluded from specific measures.

The workgroup recommended 3 measures be retired: EEG Results Reviewed, Requested, or Test Ordered (2009 Measure 3); MRI/CT Scan Results Reviewed, Requested, or Scan Ordered (2009 Measure 4); and Surgical Therapy Referral Consideration for Intractable Epilepsy (2009 Measure 6). The 2009 EEG and MRI measures were created to improve accurate diagnosis of seizure type, epilepsy syndrome, and etiology. The need for such tests remains and is reflected in the 2014 Measure 2, but this measure also requires investigating the large number of etiologies that could be investigated in specific situations. Thus, new genetic tests and tests for specific conditions such as autoimmune epilepsies may be needed to meet the 2014 Measure 2 criteria, but no specific tests are required.

Four measures were revised, and the Counseling for Women of Childbearing Potential with Epilepsy

measure was affirmed. Two new measures were approved. Screening for Psychiatric or Behavioral Health Disorders (2014 Measure 5) was created as there is now a greater appreciation of the impact of psychiatric comorbidities. The Screening for Psychiatric and Behavioral Health Disorders measure addresses the need for therapy to reduce comorbidity burden and improve quality of life.^{1,28} The 2014 Referral to a Comprehensive Epilepsy Center (2014 Measure 7) was created to encourage access to other nonsurgical interventions available at a comprehensive epilepsy center, as well as confirmation of the diagnosis and to address the prolonged wait for surgical interventions. To fulfill the measure, a referral must be considered every 2 years, but the full measure lists several exclusions, such as already being treated at a comprehensive epilepsy center (appendix e 1).

The workgroup considered several other important constructs in care for people with epilepsy, including ensuring correct diagnosis for treatment resistant (intractable) epilepsy, quality of life, and self management. These constructs were not further developed because it was determined that strong evidence was lacking, the gap in care was not large enough, or the opportunity for improvement of the measure was too low. For example, consideration was given to development of a self management measure; the workgroup did not find consensus on the presence of strong evidence or feasibility of implementing these programs. The concept will be revisited during future measurement updates for potential development as the evidence base may be strengthened. The workgroup developed a measure for a 2 year wait to withdraw anti seizure medications for children with epilepsy and with a history of focal seizures who exhibited an abnormal EEG, which was included in the draft measurement set distributed for public comment.

The workgroup announced and accepted public comments on the draft measurement set during March and April 2014. During the public comment period, 40 individuals provided 186 comments on the draft measurement set. Decisions to make changes to the proposed measures were based on a majority of comments or if comments raised concerns or issues that were not anticipated in prior discussions. As a result of public comments and concern about the existing evidence, the pediatric antiseizure medication withdrawal measure was withdrawn from the set. The full measurement set including specifications and public comments and workgroup responses is available in appendix e 1.

DISCUSSION The central purpose of the Epilepsy Update Quality Measurement Set is to improve the quality of care provided to patients. However, performance measurement alone does not improve patient

care. Quality measurement has its greatest impact when it is outcome based and linked directly to quality improvement interventions, public reporting, and payment reforms. These goals were a major focus during the revision. Quality measures are a requisite tool in high performance health care delivery. Increasingly, measures will be submitted for use in accountability programs, such as payment for reporting or quality of care and MOC. With a focus on patient centered care, federal, private, and institutional stakeholders expect stretch measures that drive ongoing practice improvement. It is imperative that the neurology and epilepsy communities lead this charge.

The AAN routinely submits developed measures to Centers for Medicare & Medicaid Services for incorporation into accountability programs. The workgroup determined that each of the updated measures is appropriate for consideration in accountability programs. In addition, the AAN will submit the updated epilepsy measures for consideration in the Physician Quality Reporting System (PQRS). From the previous epilepsy measure set, 3 measures were incorporated into PQRS.

While the goal of these measures is to help ensure quality care for epilepsy patients, there is a clear need to clinically validate these measures. The AAN promotes validation of the measures through feasibility, reliability, and validity testing and encourages health science researchers to also pursue this. In particular, it would be helpful if outcomes, either objective or patient centered, were clinically measured to establish whether adherence to these outcomes made measurable differences. Doing this research could help guide the next set of measures, as well as determine which of the measures make a clinical difference, and should be implemented as an expectation in clinical practice.

The AAN has developed performance in practice programs for MOC, NeuroPI (<http://tools.aan.com/practice/pip/>), which meets the American Board of Psychiatry and Neurology requirements for MOC Performance in Practice requirements. The NeuroPI module for epilepsy will be updated to include changes made in this measurement set. Further validation of the measurement set will be necessary. Assessment of patient outcomes after the successful implementation of these measures will provide data on their utility and determine if this improves care. According to the 2012 Institute of Medicine recommendations for epilepsy care, gaps in care need to be addressed.¹ The 2014 epilepsy measure set can assist providers in addressing these gaps for patients with epilepsy.

AUTHOR CONTRIBUTIONS

Dr. Fountain contributed to study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content,

and study supervision. Dr. Van Ness contributed to study concept and design, acquisition of data, analysis or interpretation of data, drafting/ revising the manuscript, critical revision of the manuscript for important intellectual content, and study supervision. A. Bennett contributed to study concept and design, acquisition of data, analysis or interpretation of data, drafting/ revising the manuscript, critical revision of the manuscript for important intellectual content, and study supervision. Dr. Absher contributed to study concept and design, acquisition of data, analysis or interpretation of data, drafting/ revising the manuscript, critical revision of the manuscript for important intellectual content, and study supervision. Dr. Patel contributed to study concept and design, acquisition of data, analysis or interpretation of data, drafting/ revising the manuscript, critical revision of the manuscript for important intellectual content, and study supervision. Dr. Sheth contributed to study concept and design, acquisition of data, analysis or interpretation of data, drafting/ revising the manuscript, critical revision of the manuscript for important intellectual content, and study supervision. Dr. Gloss contributed to acquisition of data, analysis or interpretation of data, drafting/ revising the manuscript, and critical revision of the manuscript for important intellectual content. Dr. Morita contributed to acquisition of data, analysis or interpretation of data, drafting/ revising the manuscript, and critical revision of the manuscript for important intellectual content. Dr. Stecker contributed to acquisition of data, analysis or interpretation of data, drafting/ revising the manuscript, and critical revision of the manuscript for important intellectual content.

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DISCLOSURE

N. Fountain serves as the vice president of the National Association of Epilepsy Centers and chair of the Epilepsy Foundation Professional Advisory Board; the University of Virginia receives research grants with Dr. Fountain as principal investigator from NIH, UCB, SK Life Sciences,

Medtronic, and Neuropace; and Dr. Fountain is an epileptologist at an epilepsy program that could potentially benefit from these quality measures by increasing referrals for a higher level of care for treatment-resistant epilepsy. P. Van Ness is an epileptologist at an epilepsy program that could potentially benefit if these quality measures increase referrals for a higher level of care for treatment-resistant epilepsy. A. Bennett and J. Absher report no disclosures. A. Patel serves on the professional advisory board for the Epilepsy Foundation of Ohio, Make-A-Wish, and the Hemispherectomy Foundation; is a consultant for Health Logix, Cyberonics, and GW Pharmaceuticals; has a research grant supported by the Pediatric Epilepsy Research Foundation; has received research support from UCB Pharma and Eisai; and is an epileptologist at an epilepsy program that could potentially benefit if these quality measures increase referrals for a higher level of care for treatment-resistant epilepsy. K. Sheth reports no disclosures. D. Gloss is a paid evidence-based medicine consultant for the American Academy of Neurology and is an epileptologist at an epilepsy program that could potentially benefit if these quality measures increase referrals for a higher level of care for treatment-resistant epilepsy. D. Morita serves on the Board of Directors and Professional Advisory Board of the Epilepsy Foundation of Greater Cincinnati and Columbus, serves as a consultant for Upsher-Smith Laboratories, receives research support from UCB, received research support from Eisai, received honoraria as a consultant for PeerView Press, and is an epileptologist at an epilepsy program that could potentially benefit if these quality measures increase referrals for a higher level of care for treatment-resistant epilepsy. M. Stecker serves as an editor for *Surgical Neurology International™ Supplement, Neuroscience Nursing*. Dr. Stecker's husband receives royalties from UpToDate in the amount of \$800. Go to Neurology.org for full disclosures.

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Quality improvement in neurology: Epilepsy Update Quality Measurement Set

Nathan B. Fountain, Paul C. Van Ness, Amy Bennett, et al.

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National Coverage Determination (NCD) 160.18 Vagus Nerve Stimulation (VNS)

MLN Matters Number: MM11461

Related Change Request (CR) Number: 11461

Related CR Release Date: May 22, 2020

Effective Date: February 15, 2019

Related CR Transmittal Number: 10145NCD

Implementation Date: June 23, 2020

PROVIDER TYPE AFFECTED

This MLN Matters Article is for physicians, providers and suppliers billing Medicare Administrative Contractors (MACs) for services provided to Medicare beneficiaries.

PROVIDER ACTION NEEDED

Change Request (CR) 11461 notifies MACs that effective for claims with dates of service on or after February 15, 2019, the Centers for Medicare & Medicaid Services (CMS) will cover Food and Drug Administration (FDA) approved vagus nerve stimulation (VNS) devices for treatment resistant depression (TRD) through Coverage with Evidence Development (CED) for patients that meet specific conditions of coverage and criteria. Please make sure your billing staffs are aware of this change.

BACKGROUND

VNS is an example of neurostimulation therapy, which targets specific regions of the brain. VNS provides indirect modulation of brain activity through the stimulation of the vagus nerve. The implanted VNS system includes a pulse generator, which is surgically inserted underneath the skin of the chest. For treatment of TRD, it is subcutaneously connected to an electrode attached to the left vagus nerve in the neck.

KEY POINTS

Section 160.18 of the [“Medicare National Coverage determination Manual”](#) establishes conditions of coverage for VNS.

The scope of this reconsideration is limited to VNS for TRD. Effective for claims with dates of service on or after February 15, 2019, CMS will cover FDA-approved VNS devices for TRD through CED when offered in a CMS-approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least one year 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. There are specific study and patient criteria that must be met.

Individuals who receive placebo VNS will be offered active VNS at the end of the trial.

VNS is non-covered for the treatment of TRD when furnished outside of a CMS-approved CED study.

All other indications of VNS for the treatment of depression are nationally non-covered.

Patients previously implanted with a VNS device for TRD may receive a VNS device replacement if it is required due to the end-of-battery life, or any other device-related malfunction. These patients do not require either ICD-10 diagnosis codes or CED-related coding. These claims will require the –KX modifier attesting to the reasonable and necessary need for the replacement device based off NCD160.18 criteria.

NOTE: VNS for medically refractory seizures and hypoglossal nerves continue to be processed as they are currently.

NOTE: A subsequent CR will be issued shortly that will provide updates to the “Claims Processing Manual” and instructions for processing claims through the CMS shared systems in regard to VNS for TRD.

ADDITIONAL INFORMATION

The official instruction, CR11461, issued to your MAC regarding this change is available at <https://www.cms.gov/files/document/r10145ncd.pdf>.

If you have questions, your MACs may have more information. Find their website at <http://go.cms.gov/MAC-website-list>.

DOCUMENT HISTORY

Date of Change	Description
June 1, 2020	Initial article released.

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A validation of the new definition of drug-resistant epilepsy by the International League Against Epilepsy

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SUMMARY

Objective: To establish applicability, the recently proposed International League Against Epilepsy (ILAE) consensus on drug-resistant epilepsy (DRE) requires testing in clinical and research settings. This study evaluates the reliability and validity of these criteria in a clinical population.

Methods: In phase I, two independent evaluators reviewed 97 randomly selected medical records of patients with epilepsy at two separate intervals. Both ILEA consensus and standard diagnostic criteria were employed. Kappa, weighted kappa, and intra-class correlation coefficient (ICC) were used to determine interobserver and intraobserver variability. In phase II, ILAE consensus criteria were applied to 250 patients with epilepsy to determine risk factors associated with development of DRE and to calculate point prevalence.

Results: The interobserver agreement of the four definitions was as follows: Berg (0.56), Kwan and Brodie (0.58), Camfield and Camfield (0.69), and ILAE (0.77). The intraobserver agreement of the four definition was as follows: Berg (0.81), Kwan and Brodie (0.82), Camfield and Camfield (0.72), and ILAE (0.82). The prevalence of DRE was the following: with the Berg's definition was 28.4%, Kwan and Brodie 34%, Camfield and Camfield 37%, and with ILAE was 33%.

Significance: This is first study to establish reliability and validity of ILAE criteria for the diagnosis of DRE. This new definition compares favorably with previously established constructs, which continue to retain clinical significance.

KEY WORDS: Drug-resistant epilepsy, Validation, Reliability, Validity, Consensus.



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Epilepsy affects 50 million people worldwide.¹ It is estimated that between 6% and 69% of patients fail to respond to standard medical and surgical therapies and continue to experience debilitating refractory seizures. These patients are classified as having drug-resistant epilepsy (DRE), a diagnosis with poor prognostic implications that include premature death, physical injury, psychosocial dysfunction, and reduced quality of life.^{2,3} The prevalence of DRE is not consistently defined and tends to vary among studies, owing to issues with population selection, sample size,

classification, terminology, and characterization of seizure intractability.^{1,4,5}

Conceptual elements of DRE are documented in the literature with terminology that is nonstandard and potentially conflicting, albeit abundant. Various prefixes such as “pharmaco-resistant-,” “refractory-,” “drug refractory-,” or “intractable-” have been applied to describe this form of epilepsy. Recognizing the need for a consistent definition to guide classification, diagnosis, epidemiology, and research, the International League Against Epilepsy (ILAE) generated the unified concept of DRE in 2008. Two years prior, Berg et al.⁶ applied six different definitions of DRE to a cohort of 613 children with newly diagnosed epilepsy. Of these six criteria, three diagnostic criteria—namely those proposed by Camfield and Camfield,⁷ Kwan and Brodie,⁸ and Berg's own^{9,10}—produced the highest observer agreement and proved credible over long-term follow-up. In 2010, an ad

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hoc ILAE task force proposed a formal consensus definition of DRE. The definition includes two levels of categorization: level 1 provides a general scheme to categorize response to each therapeutic intervention (i.e., response to antiepileptic drug (AED) trials), while level 2 provides a core definition of DRE using a set of essential criteria based on the categorization of response from level I. The task force defined DRE as the failure of adequate trials of two tolerated, appropriately chosen, and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.¹¹

The proposal represents a necessary effort toward standardization, but the authors acknowledged that empirical substantiation is needed. This study is unique as it is the first to examine the reliability and validity of the ILAE consensus definition of DRE and the first to apply these criteria to calculate the prevalence of DRE in an adult Canadian Epilepsy Centre.

METHODS

Adult patient medical records were obtained from the Saskatchewan Epilepsy Program, which serves a catchment of 1.1 million. Epilepsy syndromes and seizure types were characterized using the ILAE classification published in 1989.¹² Validation of ILAE consensus criteria for the diagnosis of DRE was performed in two phases:

Phase 1: Reliability; Intraobserver and interobserver agreement was calculated using kappa analysis for four definitions of DRE: ILAE consensus, Camfield and Camfield,⁷ Kwan and Brodie,⁸ and Berg⁹ (see Table 1 for detailed information). Two blinded, independent evaluators underwent training regarding each of the 4 definitions and variables needed to classify patients. These evaluators were not involved in patient care. Medical records from 97 patients were reviewed on two separate occasions within a time span of 2 months, to reduce the risk of patient misclassification. At the end of each chart review session, observers were asked to describe

their impression of the complexity associated with application of each definition.

Validity; Validity measurements were performed by means of correlation analysis comparing patients classified according to ILAE consensus versus the three other definitions (criterion validity) using the phi statistic (ϕ ; Table 1).

Phase 2: Prevalence; As an extension of phase I validity measurements, the ILAE consensus definition of DRE was applied to medical records of 250 randomly selected patients, obtained from a population of 800. Because the Saskatchewan Epilepsy Program is the sole epilepsy center in Saskatchewan, it was anticipated that the prevalence of DRE would range between 20% and 40%. A secondary analysis of risk factors associated with the development of DRE was also performed.

Other definitions; Developmental delay was diagnosed and classified using the Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR) criteria: mild developmental delay: intelligence quotient (IQ) 50–75, often academic skills up to grade 6 level, self-sufficient; moderate developmental delay: IQ 35–55, carries out work and self-care tasks with moderate supervision, lives within a community; severe developmental delay: IQ 20–40, masters very basic self-care skills and some communication, lives in a group home; profound developmental delay: IQ < 20–25, may develop basic self-care or communication skills. Other diagnoses such as somatic and psychiatric comorbidity were obtained from the charts.

Statistical analysis

Descriptive statistics (mean, frequencies, and proportions) were used to characterize demographic and clinical variables. For categorical and numerical variables, comparisons were made using Person's chi-square test (χ^2) and *t*-test respectively. Odds ratios (ORs) and 95% confidence intervals (Cis) were calculated to explore risk factors associated with development of DRE. Kappa coefficients (κ) were

Table 1. Definitions of drug-resistant epilepsy used in this study

Berg ⁹ (pediatric population)	The failure or lack of seizures control with more than 2 first-line antiepileptic drugs with an average of no more than 1 seizure per month for 18 months and more than 3 consecutive months seizure free during that interval
Kwan and Brodie ⁸ (children and adults)	Patients who had seizures were by definition considered to have refractory epilepsy. Seizure-free status was defined as the lack of seizures of any type for a minimum of 1 year while receiving the same dose of AED or while not taking any medication
Camfield and Camfield ⁷ (pediatric population)	Patients with an average of two or more seizures in each 2 month period during the last year of observation, despite treatment with at least three AEDs as monotherapy or polytherapy
Kwan et al. ¹¹ (children and adults)	A failure of adequate trials of two tolerated, appropriately chosen and used AED schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom. Seizure-free duration that is at least three times the longest interseizure interval prior to starting a new intervention would need to be observed or at least 12 months. The overall framework of the definition has two "hierarchical" levels: Level I provides a general scheme to categorize response to each therapeutic intervention, including a minimum dataset of knowledge about the intervention that would be needed; Level 2 provides a core definition of DRE using a set of essential criteria base on categorization of response (from Level I) to trial of antiepileptic drugs

used to assess intraobserver and interobserver agreement. The Phi coefficient was calculated to assess criterion validity.¹³ This coefficient measures the association between two binary variables and ranges from 0 to 1, where 1 indicates perfect correlation and 0 none. For all the analyses a p-value of <0.05 was considered statistically significant. Statistical analyses were carried out using IBM SPSS software (version 20; IBM Corporation, Armonk, NY, U.S.A.) and Epidat 3.1 (SERGAS-OMS, Santiago de Compostela, Spain).

RESULTS

Validation of the definition of DRE

Reliability

Interobserver agreement was moderate using Berg ($\kappa = 0.56$) and Kwan and Brodie ($\kappa = 0.58$) definitions and robust for the Camfield and Camfield ($\kappa = 0.69$) and ILAE consensus ($\kappa = 0.77$) definitions (Table 2). Patient medical records were reviewed with a difference of 35.5 ± 1.4 days between the two reviews. Intraobserver agreement was substantial for each of the four selected definitions (Berg, $\kappa = 0.81$; Kwan and Brodie, $\kappa = 0.82$; Camfield and Camfield, $\kappa = 0.72$; ILAE, $\kappa = 0.82$; Table 2).

Validity

The Phi correlation between the ILAE consensus and three standard definitions was high (ϕ -Berg = 0.75; ϕ -Camfield and Camfield = 0.81; ϕ -Kwan and Brodie = 0.93; $p < 0.001$ for all pairwise comparisons; Table 3).

Prevalence of DRE

Of 250 patients, 118 (47%) were female and 132 (53%) were male. The median age was 37.2 ± 15.6 (range 17–83) years. The median age at onset of epilepsy was 20.4 ± 17.8 (range 0–77) years. The evolution of the epilepsy was 17 ± 14 (0.92–67) years, and the mean number

Table 2. Kappa coefficients for each definition

Definition	Interobserver	Intraobserver
Berg's definition	0.56	0.81
Kwan and Brodie's definition	0.58	0.82
Camfield and Camfield's definition	0.69	0.72
ILAE	0.77	0.82

Table 3. Correlation of the ILAE definition with the other three definitions n = 250

Definition	ILAE definition	
	Phi	p-Value
Berg's definition	0.75	<0.001
Camfield and Camfield's definition	0.81	<0.001
Kwan and Brodie's definition	0.93	<0.001

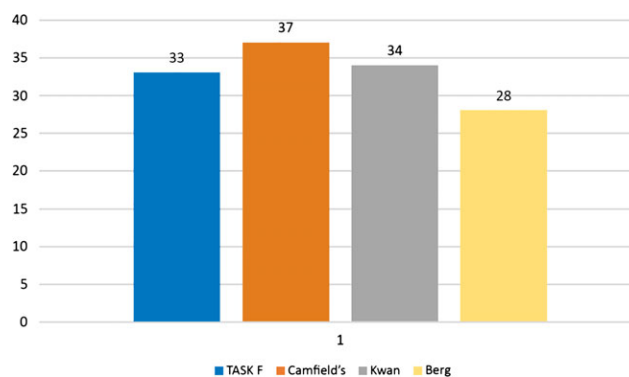


Figure 1.

In this figure the prevalence of DRE using the four definitions is displayed. The differences between rates were not statistically significant.

Epilepsia © ILAE

of AEDs used at time of evaluation was 3.2 ± 2.3 (range 0–10). The prevalence of DRE was 28.4% using Berg, 34% with Kwan and Brodie, 37% with Camfield and Camfield, and 33% using the ILAE consensus definition; this difference was not statistically significant ($p = 0.25$; Fig. 1).

Classification and etiology of Epilepsy (n = 250)

One hundred eleven patients (44.4%) had symptomatic, 119 (47.6%) had cryptogenic, and 20 (8%) idiopathic epilepsy syndromes. The etiology of epilepsy was unknown in 139 (55.4%), mesial temporal sclerosis in 27 (10.8%), cerebral neoplasm in 17 (6.8%), encephalomalacia in 11 (4.4%), cortical dysplasia in 13 (5.2%), and cranial trauma in 10 (4%). A detailed description is provided in Table 5. One hundred forty-two patients (57%) had localization-related epilepsy and 108 (43%) had generalized epilepsy. The following epilepsy syndromes were identified: Lennox-Gastaut syndrome (15 cases), juvenile myoclonic epilepsy (6), childhood absence epilepsy (4), Rasmussen's encephalitis (1), Dravet's syndrome (1), and West syndrome (1).

Analysis of patients using the ILAE consensus definition of DRE (n = 250)

Eighty-two patients (33%) were classified with DRE according to the ILAE definition. The prevalence of DRE was 39.6% in patients with symptomatic epilepsy, 28.5% in patients with cryptogenic epilepsy, and 20% in patients with idiopathic epilepsy; there was no significant differences ($p = 0.23$) between groups. The prevalence of DRE in patients with localization-related epilepsy was 37% and 28% for patients with generalized epilepsy; there was no significant differences between groups.

Compared to other epilepsy patients, patients with DRE were diagnosed with epilepsy at a younger age and demonstrated longer evolution of epilepsy. Age and sex were not significantly associated with development of DRE. Any developmental delay (OR 4.3, CI 2.2–8.4,

Table 4. Comparison of patients with and without DRE (n = 250) using the ILAE's definition

Prognostic factors	No DRE (%) n = 168	DRE (%) n = 82	OR (intervals)	p-Value
Female	83 (49)	35 (43)	0.76 (0.45–1.30)	0.32
Mean age, years \pm SD ^a	37.4 \pm 16.3	36.2 \pm 13.9	NC	0.53
Mean age at onset of epilepsy \pm SD ^a	23.8 \pm 18.8	13.6 \pm 13.5	NC	<0.001
Age at onset \leq 12	47 (28)	45 (55)	3.1 (1.8–5.3)	<0.001
Means years of epilepsy evolution \pm SD ^a	14.2 \pm 13.2	22.6 \pm 14.0	NC	<0.001
Mean number of AEDs on \pm SD ^a	2.5 \pm 1.7	5.4 \pm 2	NC	<0.001
Psychiatric comorbidity	28 (17)	15 (18)	1.1 (0.56–2.2)	0.75
Diagnosis of autism	0	6 (7)	NC	NC
Diagnosis of developmental delay (any severity)	18 (11)	28 (34)	4.3 (2.2–8.4)	<0.001
Profound developmental delay	6 (3.6)	9 (11)	3.3 (1.1–9.6)	0.02
Presence of any epileptic syndrome	13 (7.7)	15 (18.3)	2.7 (1.2–5.9)	0.01

NC, not calculated because one of the cells has a zero value; SD, standard deviation.
^at-Test analysis.

Table 5. Comparison of patients with and without DRE (n = 250) using the ILAE's definition

Classification factors	No DRE (%) n = 168	DRE (%) n = 82	OR (confidence intervals)	p-Value
Etiology				
Unknown	100 (59.5)	39 (47.6)	0.6 (0.3–1)	0.074
MTS	11 (6.5)	16 (19.5)	3.4 (1.5–7.8)	0.002
Cortical dysplasia	13 (57.7)	8 (9.8)	1.2 (0.5–3.2)	0.59
Encephalomalacia	8 (4.8)	3 (3.7)	0.8 (0.2–2.9)	0.69
Cerebral neoplasm	12 (7.1)	5 (6.1)	0.8 (0.3–2.5)	0.76
Cranial trauma	7 (4.2)	3 (3.7)	0.9 (0.2–3.4)	0.85
Congenital malformation	4 (2.4)	4 (4.9)	0.7 (0.6–0.7)	0.11
Cerebral infection	2 (1.2)	5 (6.1)	5.4 (1–28)	0.02
Stroke	5 (3)	0	NC	0.11
Genetic	4 (2.4)	1 (1.2)	0.5 (0.05–4.6)	0.54
AVM	3 (1.8)	0	NC	0.22
Asphyxia during birth	0	2 (2.4)	NC	0.042
Gliosis	2 (1.2)	0	NC	0.32
Autoimmune	1 (0.6)	0	NC	0.48
Localization				
Localization related	90 (53.5)	52 (62.5)	0.6 (0.3–1.1)	0.14
Temporal	52 (31)	30 (36.5)	1.2 (0.7–2.2)	0.4
Frontal	16 (9.5)	9 (11)	1.2 (0.5–2.7)	0.7
Frontotemporal	9 (5)	5 (6)	1.1 (0.4–1.9)	0.8
Other	9 (5)	8 (10)	1.9 (0.71–5)	0.1
Generalized	78 (46)	30 (36.6)	0.66 (0.39–1.1)	0.14
Epileptic syndromes				
Symptomatic	67 (40)	44 (54)	1.75 (1.02–2.98)	0.04
Cryptogenic	85 (51)	34 (41)	0.69 (0.4–1.18)	0.17
Idiopathic	16 (9)	4 (5)	0.48 (0.16–1.51)	0.24
Lesional (MRI)	57 (45.6)	41 (63)	2.0 (1.1–3.7)	0.02

NC, not calculated because one of the cells has a zero value; AVM, arteriovenous malformation; MTS, mesial temporal sclerosis.

p 0.001), profound developmental delay (OR 3.3 CI 1.1–9.6, p 0.02), presence of epileptic syndrome (OR 2.7, CI 1.2–5.9, p 0.02), magnetic resonance imaging (MRI) evidence of cortical dysplasia (OR 3.4, CI 1.5–7.8, p 0.002), and lesional epilepsy as demonstrated by MRI (OR 2.0, CI 1.1–9.6, p 0.02) significantly increased the risk of DRE (Tables 4 and 5).

DISCUSSION

With the advancement of medical, surgical, and neuro-modulatory approaches, the importance of prompt diagnosis of DRE has assumed heightened significance.^{1,14} The development of the ILAE consensus definition for DRE was motivated by the need to facilitate research

and inform clinical practice through the formulation of a readily applicable and conceptually consistent framework. Although the ILAE consensus definition provides a standardized context, the ad hoc committee acknowledged that studies are needed to demonstrate its suitability in clinical practice and research setting. The present study was conducted in an attempt to address this issue and constitutes the first evaluation of the validity of ILAE diagnostic criteria for DRE. The successful validation of the ILAE definition of DRE has far reaching implications for the design and conduct of randomized controlled trials, epidemiological studies, diagnosis time frames, treatment considerations, and resource allocation in health care systems.¹³

Ramos-Lizana et al.¹⁵ assessed the prevalence of DRE in 508 pediatric patients with newly diagnosed epilepsy at a tertiary referral center. Patients were followed for at least 90 months and were classified using the ILAE consensus definition. In this cohort, 87 (19%) patients eventually met criteria for DRE, leading authors to suggest that this new classification scheme captures a larger population at risk. Martinez-Juarez et al.¹⁶ retrospectively assessed 206 patients and determined that 57 (28%) were seizure free, 115 (56%) were not, 17 (8%) were classified as undetermined, and 17 (8%) were pseudo-refractory. The prevalence of DRE was high at 56%. In these two studies, no comparison was made between the various definitions of DRE, and validation was not performed.

The primary aim of this study was the validation of a new definition of DRE that is poised to shape ongoing research and clinical decision making. In interobserver and intraobserver comparisons, the ILAE definition obtained the highest kappa scores (0.77 and 0.82), thus proving its reliability. Similarly, the excellent interobserver agreement of the ILAE definition was recently demonstrated by Hao et al.,¹⁷ whose results yielded a kappa score of 94%. However, it was also found that the Camfield and Camfield, Kwan and Brodie, and Berg et al. definitions met criteria for reliability and validity. These results are confirmatory to those of a prior study, which taken together suggest that these three definitions continue to hold clinical significance.⁶ The calculation of the ϕ -statistic demonstrated that ILAE consensus definition had an excellent correlation with the three preselected DRE diagnostic criteria, corroborating that all diagnostic criteria capture the same population at risk and facilitate accurate diagnosis.

Point prevalence was calculated in phase II. It should be noted that the present study is the first assessment of the prevalence of DRE in a Canadian adult population. Our center is the only tertiary epilepsy referral center in the province of Saskatchewan, and we were expecting a high prevalence of DRE. The utilization of the four definitions demonstrated a point prevalence between 28.4% and 37% (the difference was not statistically significant), which concords with our a

priori hypothesis and matches figures reported by other tertiary referral centers.^{8,14} This finding is reassuring and in our view provides validation of the ILAE consensus definition. Ultimately, this investigation provides evidence that all four definitions provide adequate estimations of DRE and are readily amenable to clinical population studies in epilepsy clinics and centers.

Our study reveals a mean DRE prevalence of 33%, which is almost threefold higher than the 12.4% value reported by Camfield⁷ in a pediatric population. This difference is likely attributable to the presence of a large percentage of benign pediatric epileptic syndromes.

Certain features of our study are instructive for future research. We provide proof of concept that the ILAE diagnostic criteria provide reliable diagnosis of DRE in the setting of retrospective chart review, a strategy that has been applied in earlier studies using prior diagnostic definitions.¹⁸ A key strength of this study, emanating from our center's status as the sole epilepsy program in our province, was the ability to construct comprehensive patient records based on continuous follow-up by the same physician(s). This enabled efficient data extraction while reducing the risk of classification bias. Such a setup is a rarity, as most patients with epilepsy are seen by different physicians in different hospitals.¹⁸ For instance, Carreño et al. performed a retrospective study of 40 patients admitted to an epilepsy monitoring unit for pre-surgical evaluation but were able to classify only 13 patients (32.5%). The majority of patients could not be classified due to insufficient information concerning AED usage and dosing.

The two evaluators considered application of the ILAE consensus to be more time-intensive due to the need to gauge more variables. However, they considered this definition to better classify patients and as providing greater diagnostic certainty of DRE. By contrast, the evaluators felt that the information needed to apply the Camfield and Camfield and Kwan and Brodie definitions was easy to extract from patient medical records, although they felt that some patients could not be accurately classified. The Berg definition was found to be the most difficult to apply. Fundamentally, however, all definitions provided high scores of agreement and generated similar prevalence rates.^{9,19} The time needed to extract relevant variables is thus a limitation of the ILAE consensus criteria and should be factored into the design of epidemiological studies, surveys, and interviews.

Strengths of the present investigation include its methodology and resultant elucidation of strong intraobserver and interobserver agreement between three widely used and ILAE consensus definitions. Due to the lack of a gold standard to define DRE, the methodology used in this study was the only option for validating the definition.¹³ The corroboration of a high prevalence of epilepsy in our center is an important aspect of the validation.

Limitations of this study are its retrospective design, reliance on patient medical records as the sole source of information, which could potentially bias application of case definitions due to incomplete availability of information. Our validation study was a cross sectional study and the status of DRE was assessed at the time that the time of chart review. Our results are applicable only to adult populations, as children were not included. Future studies are required to validate the definition in other settings and with other methodologies.

CONCLUSION

The ILAE consensus definition of DRE was found to be valid and reliable. It is applicable to retrospective study design, provided that all necessary variables required to classify patients are present. Prior definitions of DRE proposed by Camfield and Camfield, Berg and Kwan, and Brodie also retain clinical validity.

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DISCLOSURE OR CONFLICT OF INTEREST

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SPECIAL REPORT

Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

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SUMMARY

To improve patient care and facilitate clinical research, the International League Against Epilepsy (ILAE) appointed a Task Force to formulate a consensus definition of drug resistant epilepsy. The overall framework of the definition has two “hierarchical” levels: Level 1 provides a general scheme to categorize response to each therapeutic intervention, including a minimum dataset of knowledge about the intervention that would be needed; Level 2 provides a core definition of drug resistant epilepsy using a set of essential criteria based on the categorization of response (from Level 1) to trials of

antiepileptic drugs. It is proposed as a testable hypothesis that drug resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. This definition can be further refined when new evidence emerges. The rationale behind the definition and the principles governing its proper use are discussed, and examples to illustrate its application in clinical practice are provided.

KEY WORDS: Epilepsy, Drug resistance, Refractory, Intractable, Definition, ILAE.

Although the concept of drug resistant (often used interchangeably with “medically refractory/intractable” or “pharmacoresistant”) epilepsy may appear self-explanatory and intuitive, a precise definition has remained elusive. This has resulted in diverse criteria used by different clinicians and researchers, or even a lack of explicit criteria in some cases, rendering it difficult to compare findings

across studies and to make practice recommendations (Perucca, 1998; Tanganelli & Regesta, 1999; Berg et al., 2006; Kwan & Brodie, 2006; Arzimanoglou & Ryvlin, 2008). In response to this situation, the International League Against Epilepsy (ILAE) appointed a Task Force under the Commission on Therapeutic Strategies to formulate a proposal for a consensus definition of drug resistant epilepsy. The Task Force comprised members with diverse expertise, including epidemiology, adult and pediatric epileptology, neurosurgery, clinical pharmacology, and clinical trial design. Pertinent literature and discussion at relevant workshops (Kahane et al., 2008) were considered. This report sets out the proposed definition, the rationale behind it, the principles governing its proper use, and examples to illustrate its application in clinical practice. The report was circulated to all ILAE Commissions for

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comment and was approved by the Executive Committee of the ILAE during the 28th International Epilepsy Congress in Budapest, Hungary, June 28th to July 2nd, 2009. It should be emphasized that given the paucity of high quality data on the long-term prognosis of epilepsy, the proposed definition should not be regarded as a foregone conclusion, but is intended to represent a consensus opinion that needs to be tested in rigorous prospective studies and refined as new evidence emerges.

Any definition of drug resistant epilepsy should be understood and applied within the context of its intended use, because different definitions may be required for different purposes. The primary goal of this consensus definition is to improve patient care and facilitate clinical research. As such, by setting out the minimum criteria for defining drug-resistant epilepsy, it aims to serve as a working definition that is pragmatic and applicable for everyday clinical management. Fulfillment of the definition in a patient should prompt a comprehensive review of the diagnosis and management, preferably by an epilepsy center. In addition, by applying the definition, practitioners (and patients) can be alerted to the type of information that should be collected during clinical consultation.

The primary target users of the definition are medical practitioners at all health care levels (including primary care practitioners, general neurologists, and epileptologists) directly involved in the clinical care of people with epilepsy. With the appropriate information collected on treatment response, we believe the definition may aid nonspecialists in recognizing patients with drug resistant epilepsy for prompt referral to specialist centers for evaluation. Other target users are clinical researchers, because adoption of a consensus definition will facilitate comparison and meaningful synthesis of results across studies. The definition may also be valuable to patients and their caretakers, as well as other interest groups such as scientists in basic research, government regulators, legislators, health care administrators, insurers, educators, and employers.

FRAMEWORK OF DEFINITION

The overall framework of the definition comprises two “hierarchical” levels: Level 1 provides a general template or scheme to categorize outcome to each therapeutic intervention (whether pharmacologic or nonpharmacologic), including a minimum dataset about the intervention that would be needed for such purpose. Broadly, the categories of outcome include “seizure-free,” “treatment failure,” and “undetermined,” which are elaborated below. Level 1 forms the basis for Level 2, which provides a core definition of drug resistant epilepsy based on how many “informative” trials of antiepileptic drugs (AEDs) resulted in a “treatment failure” outcome (as defined in Level 1). This core definition may then be adapted, where appropriate, for specific purposes or clinical scenarios.

LEVEL 1: CATEGORIZATION OF OUTCOME TO A THERAPEUTIC INTERVENTION

There are many dimensions in a patient’s outcome to a given therapeutic intervention. The categorization scheme should be simple and practical, rather than exhaustive, to facilitate its use across a broad range of clinical and research settings. Therefore, the proposed scheme contains the two most clinically relevant outcome dimensions, namely, seizure control and occurrence of adverse effects (Table 1). Outcomes to a given intervention are categorized based on whether it rendered the patient seizure-free (Category 1) or not (Category 2). For the outcome to fall into either category, the intervention must be “appropriate” and “adequate,” each of which is defined in subsequent text of this article. Otherwise, the outcome is designated as undetermined (Category 3). Each category is then subdivided into A, B, and C, based on outcome with respect to adverse effects. This subdivision is included even though it does not contribute to the definition of drug resistance, because there is an important clinical difference between a seizure-free patient without any adverse effects, and one who is seizure free at the expense of substantial adverse effects. Capturing this information may aid clinicians in deciding interventions. The appropriate application of the scheme is based on the following assumptions and provisions.

Appropriateness of intervention

To be regarded as an intervention in the scheme, it must be “appropriate” for the patient’s epilepsy and seizure type. An “appropriate” intervention should have previously been shown to be effective, preferably in randomized controlled studies, which provide the highest level of evidence. Instead of listing all “appropriate” interventions, it is suggested that

Table 1. Scheme for categorizing outcome of an intervention for epilepsy

Outcome dimension ^a		
Seizure control	Occurrence of adverse effects	Outcome category
1. Seizure-free	A. No	1A
	B. Yes	1B
	C. Undetermined	1C
2. Treatment failure	A. No	2A
	B. Yes	2B
	C. Undetermined	2C
3. Undetermined	A. No	3A
	B. Yes	3B
	C. Undetermined	3C

^aSee text for definitions of “seizure-free,” “treatment failure,” and “undetermined.” The numeric and alphabetic nomenclature of categories does not imply gradation or hierarchy.

anyone using this scheme justify their choices in this regard. For instance, ethosuximide would usually not be considered an appropriate intervention for focal seizures. Under most circumstances, a trial of this drug in a patient with focal epilepsy would not “count” toward being defined as “drug resistance.”

“Adequate/informative” versus “uninformative” trial

In addition to being “appropriate,” the intervention must have been applied “adequately” for a valid assessment of the treatment outcome. In general, this requires application of the intervention at adequate strength/dosage for a sufficient length of time. This may not be the case in some circumstances, for example, when a drug is withdrawn before it has been titrated to its clinically effective dose range because of an adverse effect. Although the drug has “failed” (i.e., it is not a suitable intervention for the patient), the “failure” was not because of lack of efficacy for seizure control. Such an outcome may have little bearing on the efficacy of other AEDs and generally is not considered as part of “drug resistance” per se. In these situations, outcome of the intervention in terms of seizure control should be categorized as “undetermined.” If the patient is lost to follow-up before outcome to an intervention can be evaluated, then seizure control and occurrence of adverse effects will both be considered “undetermined.”

Given the wide interindividual variation in the doses required to achieve seizure freedom (Kwan & Brodie, 2001), it is difficult to rigidly define the “clinically effective dose range” for each AED. This is further confounded by multiple internal and external factors, including the setting in which the AED is used (monotherapy or polytherapy), the age of the patient, and the presence of hepatic or renal impairment, which may affect drug clearance. As an example, for adults, reference may be made to the World Health Organization (WHO)’s defined daily dose (DDD), which is the assumed average maintenance dose per day for a drug used for its main indication (World Health Organization, 2008). It is important to note that there should be a documented attempt to titrate the dose to a target clinically effective dose range, particularly for AEDs, the tolerability of which is strongly dependent upon gradual titration (Perucca et al., 2001).

Table 2 lists the minimum dataset required to determine whether the trial of an intervention is informative in an individual patient. In the absence of this dataset, the response should be considered undetermined. In practice, the data may be adequate for assessing adverse effects but not seizure control, or vice versa. This is acknowledged in the scheme in Table 1.

Seizure freedom and treatment failure

Lifelong seizure freedom without adverse effects can be considered the most clinically relevant outcome of any intervention for epilepsy (Sillanpää et al., 2004; Vickrey

Table 2. Minimum dataset required to determine whether the trial of a therapeutic intervention is informative

Nature of the intervention (e.g., type of drug, in the case of antiepileptic drug treatment)
Mode of application (e.g., formulation, dose, dosing interval, and patient’s compliance in case of an antiepileptic drug)
Duration of exposure
Occurrence of seizures and adverse effects during the trial period
Whether there was any effort to optimize dose
Reason(s) for discontinuation (if applicable)
Unsatisfactory seizure control
Adverse effects
Long-term seizure freedom
Psychosocial reasons, for example, planning for pregnancy
Administrative reasons, for example, lost to follow up
Financial issues, for example, cannot afford treatment
Patient/caretaker preference
Other reasons

et al., 1995; Jacoby et al., 2007; Téllez-Zenteno et al., 2007). Therefore, under the scheme, seizure outcome is dichotomized into seizure-free (Category 1) or treatment failure (Category 2). The term “seizure-free” refers to freedom from all seizures, including auras. It is acknowledged that different seizure types in different individuals may be associated with variable degrees of impact, which is a matter of appreciation and would be taken into account by the treating clinician when deciding the most appropriate course of action for the patient. Therefore, for practicality, occurrence of any seizure is regarded to indicate failure of the treatment to lead to seizure freedom.

Breakthrough seizures that occur in temporal proximity to potentially seizure provoking external factors such as sleep deprivation, menstruation, intercurrent febrile illness, and so on, pose difficulties in categorization because the causal association between the external factor and the seizure is often uncertain. In general, seizures that occur under these circumstances should still be considered as evidence of inadequate seizure control and hence treatment failure, but seizure relapse due to poor treatment compliance should not.

In deliberating what constitutes an adequate period without seizures for a patient to be regarded as “seizure-free,” two main factors were considered. First, the duration of follow-up required to determine whether a therapeutic intervention has had an appreciable impact on seizure occurrence is dependent on the preintervention seizure frequency. For instance, it would not be surprising for a patient with only one seizure in the previous year to remain seizure-free for the next 6 months after starting a new intervention, but it would be premature and unwarranted to claim that the therapeutic intervention is responsible for a patient’s freedom from seizures until sufficient time has passed.

The “rule of three” for calculating confidence intervals for zero events can be used in this setting (Hanley & Lippman-Hand, 1983). To be 95% certain that a patient’s seizure frequency has at very least decreased (i.e., there has been some therapeutic effect), a seizure-free duration that is at least three times the longest interseizure interval prior to starting a new intervention would need to be observed. For example, if prior to the intervention the patient had intervals without seizures of up to 6 months, a seizure-free period of 18 months would be required to reasonably conclude that his seizure frequency is lower than that prior to the intervention. It should be noted that, in theory, patients with even more infrequent seizures would have to be followed up for many years to determine whether their seizures had truly come under control. This is not practical, either in research or clinical settings. For this reason we recommend that three times the longest interseizure interval be used as an indicator of positive treatment response. Given that an initiation or change of intervention regimen is often not indicated for seizures occurring less than once per year, the longest preintervention interseizure interval should be determined from seizures occurring within the preceding 12 months. For practical purpose, interseizure interval should be derived according to days on which one or more seizure has occurred. Obviously, at least two seizures must have been documented to determine the preintervention interseizure interval; therefore, this approach cannot be applied to a patient treated after a single seizure.

The other main consideration is the need to document a sustained response that is clinically meaningful. Studies including patients treated medically (Sillanpää & Shinnar, 2005; Jacoby et al., 2007) or surgically (Markand et al., 2000; Spencer et al., 2007) show that absolute seizure freedom, usually taken as at least 12 months, is the only relevant outcome consistently associated with meaningful improvement in quality of life. In a community-based survey, patients with one or more seizures over the last 2 years had higher levels of anxiety and depression, greater perceived stigma and impact of epilepsy, and lower employment rates than did those who were seizure-free (Jacoby et al., 1996). In many countries, having even one seizure per year poses restrictions on driving (Fisher et al., 1994; Berg & Engel, 1999). Therefore, there was consensus that seizure-free duration should be at least 12 months.

Based on the preceding consideration, seizure freedom (Category 1 outcome) is defined as freedom from seizures for a minimum of three times the longest preintervention interseizure interval (determined from seizures occurring within the past 12 months) or 12 months, whichever is longer. On the other hand, treatment failure (Category 2 outcome) is defined as recurrent seizure(s) after the intervention has been adequately applied (as defined earlier). If a patient has been seizure-free for three times the preintervention interseizure interval but for <12 months, seizure control should be categorized as “undetermined.” However, if

the patient experiences another seizure before the end of the 12-month period, the treatment is considered “failed,” even though the seizure frequency has reduced compared with baseline. We acknowledge that a therapeutic intervention may lead to a clinically meaningful reduction in seizure frequency (or severity) that stops short of seizure freedom. Categorization of such a response may be considered at a later date for incorporation into the scheme.

Occurrence of adverse effects

By adapting the WHO’s definition of adverse drug reaction (World Health Organization, 1972), an adverse effect to any therapeutic intervention for epilepsy may be defined as “any response to an intervention which is noxious and unintended, and which occurs when the intervention is applied with modalities normally used in humans for the treatment of epilepsy.” The WHO definition has generally been interpreted as implying that there should be no error in the use of the intervention (Leape, 1995; Edwards & Aronson, 2000), an important consideration that is consistent with the concept of “appropriateness” of intervention, as already discussed.

Assessing adverse effects is fraught with difficulties, and some elements of subjectivity are unavoidable. Critical issues in the assessment are the methodology used to detect and quantify adverse effects, and the criteria applied to establish the causality link with the applied intervention. In particular, relying on unstructured interviews and a general medical examination may lead to underestimation of adverse effects, whereas the use of checklists and questionnaires can lead to overestimation (Baker et al., 1998; Carreño et al., 2008). Some important adverse effects, such as vigabatrin-induced visual field defects, may only be identifiable with specialized laboratory tests (Wild et al., 2007). Algorithms for causality assessment have been developed (Karch & Lasagna, 1977; Edwards & Aronson, 2000). Even when causality has been established, assessing the clinical impact of an adverse effect on the individual’s well being or quality of life is a challenging task. In most clinical situations, however, treating physicians can make a reasonable subjective judgment based on results of medical examination and interviews with patient and family members, and we suggest that such judgment be applied when categorizing the presence or absence of adverse effects in response to an intervention.

Other dimensions of outcome

For practical purposes, other dimensions of outcome are not included in the current scheme, but their importance is recognized and they may be incorporated into future schemes. These dimensions may include factors such as psychosocial outcomes and level of patient satisfaction. A variety of quality of life scales have been developed and are widely applied in research settings (Leone et al., 2005). From a patient-centered care perspective, patients’

satisfaction with an intervention should be the final arbiter in defining its success or failure. Patients' satisfaction extends beyond measurement of seizure control, adverse effects, or quality of life scores, and may be influenced by a broad range of internal and external variables, such as, in the case of epilepsy surgery, preoperative expectations, postoperative affect, ability to discard the sick role, subsequently obtaining employment, and perceived success (Wass et al., 1996; Wilson et al., 1999; Reid et al., 2004; Chin et al., 2006). Although the construct of patient satisfaction with an intervention is multifaceted and complex, it has been successfully evaluated using simple, single-item, or few-item rating scales, such as dichotomous yes/no questions, or graded point scales. Clinicians may be encouraged to include one of these measures in their assessment when assessing success or failure of an intervention and in clinical decision making.

LEVEL 2: DEFINITION OF DRUG RESISTANT EPILEPSY

Drug responsiveness of a patient's epilepsy should be regarded as a dynamic process rather than a fixed state. Instead of being constant, the course of epilepsy sometimes fluctuates (Berg et al., 2009), and apparent changes in responsiveness to AED treatment may merely represent shifts in the pathophysiology of the underlying disorder. The classification of a patient's epilepsy as drug resistant at a given point in time is valid only at the time of the assessment and does not necessarily imply that the patient will *never* become seizure-free on further manipulation of AED therapy (Huttenlocher & Hapke, 1990; Berg et al., 2001, 2006; Callaghan et al., 2007; Luciano & Shorvon, 2007; Schiller & Najjar, 2008).

The number of AEDs that needs to have failed for the epilepsy to be defined as drug resistant was extensively debated within the Task Force. An implicit assumption in any definition is that seizure freedom will not or is very unlikely to be attained with further manipulation of AED therapy. Therefore, any definition must be based on an assessment of the probability of subsequent remission after each drug failure. Ideally, the evidence should be derived from large-scale, prospective, long-term, population-based studies including both adults and children at the point of diagnosis or treatment initiation, and should be based on an assessment of outcome after failure of successive informative AED trials. Few, if any, studies in the literature meet such requirement. Observational cohort studies of newly diagnosed epilepsy in adults (Kwan & Brodie, 2000; Mohanraj & Brodie, 2006) and children (Arts et al., 2004) suggest that once a patient has failed trials of two appropriate AEDs, the probability of achieving seizure freedom with subsequent AED treatments is modest. Recent studies appear to suggest that a proportion of these patients may still become seizure-free with subsequent drug manipulation (Callaghan et al., 2007; Luciano &

Shorvon, 2007), but these studies were retrospective and sampled prevalent cases, and did not take into account the reasons for failure which, as already discussed, may indicate that the AEDs have not been adequately tried. A recent report from a prospective study in children documented that although many patients who had failed two informative trials of AEDs had periods of seizure freedom with further drug trials, lasting remission remained elusive (Berg et al., 2009).

On the basis of a careful deliberation of the available evidence, building on Level 1 of the definition framework, for operational purposes, the following definition is proposed:

Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.

It should be stressed that the consensus to adopt the failure of two (rather than greater numbers) AED schedules in the definition represents a testable hypothesis and aims to avoid unnecessary delay in evaluation, and may be revised as more high quality data become available.

In addition to number of AEDs failed, two other elements are most commonly included in definitions of drug resistant epilepsy in the literature, namely, the frequency of seizures and duration of follow-up. In the proposed definition, "failure" and "sustained seizure freedom" are as defined in Level 1 (categorization of intervention outcome) of the definition framework, which already incorporates seizure frequency and treatment duration, so that separate criteria for these elements are redundant. Applying the categorization of intervention outcome (Table 1), drug resistance is defined as having Category 2 outcome for trials of at least two AEDs (monotherapies or in combination) without a Category 1 outcome on the drug(s) currently taken. Drug resistance should be defined only by informative trials, that is, the two AEDs should have been appropriately chosen and adequately tried, and that none of the outcomes that will be counted toward the two drug failures should be "undetermined." In other words, some patients may "fail" many AEDs before they fail two that are "appropriate" and in a way that is "informative."

Drug-responsive epilepsy and apparent fluctuation in drug responsiveness

It follows from Level 1 of the definition framework that a person's epilepsy can be classified as "drug responsive" if he/she is having a Category 1 outcome to the current AED regimen, that is, he/she has been seizure-free for a minimum of three times the longest pretreatment interseizure interval, or 12 months, whichever is longer.

During its long and sometimes fluctuating course a person's epilepsy may not fulfill the definition criteria for either drug resistant or drug-responsive epilepsy at certain time points. In such circumstances, drug responsiveness

Table 3. Examples of how the definition framework can be applied in different clinical scenarios

Patient history	Narrative drug	Level 1—categorization of treatment outcome	Level 2—classification of drug responsiveness of epilepsy	Notes
1	A patient had one seizure in January 2006 and two seizures in October 2006. After starting treatment in November 2006 he has been seizure free for 30 months with no adverse effect	One current drug with seizure-free outcome (Cat. 1A)	Drug responsive	The longest pretreatment interseizure interval was 9 months (January–October 2006). The patient has had no seizure for more than three times the pretreatment interseizure interval and for more than 12 months
2	A 16-year-old patient was started on valproate 2 years ago after experiencing two seizures in 6 months, and has been seizure-free since with mild sedation. He reports a history of an apparently nonfebrile convulsive seizure when he was 6 years of age	One current drug with seizure-free outcome (Cat. 1B)	Drug responsive	The longest pretreatment interseizure interval was 6 months. The patient has had no seizure for more than three times the pretreatment interseizure interval and for more than 12 months. The seizure that occurred at 6 years of age (more than 12 months prior to starting treatment) is not relevant to determining the responsiveness of his current epilepsy
3	A 40-year old man was diagnosed to have partial epilepsy 20 years ago. He reported “I was on phenytoin initially for a short period, it didn’t work and they took me off.” He was then given an adequate trial of carbamazepine but continued to have monthly seizures. Levetiracetam was added 1 year ago and tried adequately. He now has seizures once every 3 months	One previous drug with undetermined outcome (Cat. 3C). Two current drugs with treatment failure outcome (Cat. 2)	Drug resistant	Outcome of phenytoin treatment was undetermined because of lack of sufficient data (see Table 2). Nonetheless, he has failed informative trials with two appropriate AEDs. Treatment with levetiracetam is considered failed because despite reduction in seizure frequency, seizure free duration is <12 months
4	A patient was newly started on carbamazepine after two partial seizures in 9 months. He has had no seizures for 12 months since	One current drug with undetermined outcome (Cat. 3)	Undefined	The pretreatment interseizure interval was 9 months. Although the patient has had no seizure for 12 months, the duration is less than three times the pretreatment interseizure interval, hence outcome to treatment is undetermined and drug responsiveness of epilepsy is undefined
5	A 16-year-old girl was started on carbamazepine a week after she had a tonic-clonic seizure in the morning, with a history (not recognized by her doctor at the time) of jerks over the past 3 months. The jerks got worse after 2 months on carbamazepine 800 mg/day. EEG later showed generalized polyspike and wave discharge. She was diagnosed to have juvenile myoclonic epilepsy and was switched to lamotrigine, which was stopped after 2 weeks (dosage at the time, 50 mg/day) because of a rash. She is now on valproate 2 g/day for 3 months, but occasional jerks continue	One previous inappropriate drug. One previous drug with undetermined outcome (Cat. 3B). One current drug with treatment failure outcome (Cat. 2)	Undefined	Carbamazepine is recognized to exacerbate myoclonic seizures and, in this case, is not considered an appropriate treatment for the patient’s epilepsy syndrome. Lamotrigine and valproate are appropriate treatments, but outcome in terms of seizure control of lamotrigine is undetermined because it was stopped due to an adverse effect during titration, before a dose range usually regarded as optimal could be reached. Thus the patient has failed only one drug (valproate) so far, and the drug responsiveness of her epilepsy remains undefined
6	A patient is having more than one seizure per day for 3 months despite adequate trials of four appropriate AEDs. Patient is taking one drug currently	Three previous drugs and one current drug with treatment failure outcome (Cat. 2)	Drug resistant	The patient has failed more than two appropriate AEDs

Continued

Table 3. Continued.

Patient	Narrative drug history	Level 1—categorization of treatment outcome	Level 2—classification of drug responsiveness of epilepsy	Notes
6	After adding drug X, patient 6 has had no seizure for 8 months	Four previous drugs with treatment failure outcome (Cat. 2). One current drug with undetermined outcome (Cat. 3)	Drug resistant	Outcome of treatment with drug X is undetermined and the epilepsy remains drug resistant because the patient has not been seizure-free for 12 months
6	With further follow-up patient 6 has had no seizure for 24 months	Four previous drugs with treatment failure outcome (Cat. 2). One current drug with seizure-free outcome (Cat. 1)	Drug responsive	The patient has had no seizures for more than three times the pretreatment interseizure interval and for more than 12 months
6	Patient 6 has two seizures within 1 month	Four previous drugs and one current drug with treatment failure outcome (Cat. 2)	Undefined	The patient is no longer seizure free, treatment of drug X is failed, but the “clock” is “reset” for considering the epilepsy to be drug resistant again in future after it has been drug responsive. Thus at present the epilepsy does not fulfill the criteria of drug resistant (unless the patient fails at least one further drug after the relapse)
6	Two more appropriate AEDs are added at adequate dosage but patient 6 continues to have seizures once per month	Four previous drugs and three current drugs with treatment failure outcome (Cat. 2)	Drug resistant	After the relapse the patient has failed more than two adequate trials of appropriate AEDs

AED, antiepileptic drug; EEG, electroencephalography.

should be temporarily classified as “undefined.” This occurs, for instance, in a newly diagnosed patient who has not experienced the duration required for defining seizure freedom, or in a patient who has failed informative trials of less than two AEDs.

Other scenarios that pose difficulty in classification occur when there appears to be a change in drug responsiveness of the epilepsy during its dynamic course. In these scenarios the classification should be reviewed and revised accordingly. For instance, a patient with drug-resistant epilepsy stops having seizures upon receiving a new AED regimen but the duration does not yet meet the criteria for defining seizure freedom. For clarity, it is proposed that outcome of the individual drug (Level 1) should be categorized as “undetermined” and the overall drug responsiveness (Level 2) should remain as drug resistant unless and until sufficient time has passed to reclassify the epilepsy as drug responsive (i.e., seizure-free for three times pretreatment interseizure interval, or 12 months, whichever is longer).

In the opposite scenario, epilepsy relapses in a seizure-free patient. In this situation clearly the epilepsy is no longer drug responsive, but it can only be considered drug resistant if it subsequently meets the criteria for resistance. It is proposed that, if only one seizure has recurred, the outcome of the individual drug (Level 1) should be categorized as

“undetermined” and the overall drug responsiveness (Level 2) should be classified as “undefined.” If two seizures have recurred, outcome to the individual drug(s) should be categorized as treatment failure, and the overall drug responsiveness remains “undefined.” If an additional AED is adequately tried and failed, then the epilepsy is redefined as drug resistant. If the patient has had no further seizure for three times the interseizure interval (of the relapsed seizures) or 1 year, whichever is longer, the epilepsy is redefined as drug responsive. It is proposed that this classification approach also applies to the scenarios where the epilepsy had been drug resistant before the patient became seizure free. Because there is a paucity of data on the seizure pattern in such scenarios it is acknowledged that such a classification approach is largely empirical and needs to be tested for its validity in prospective studies.

APPLICATION OF THE DEFINITION IN SPECIFIC SCENARIOS

We recommend application of the consensus definition to diverse clinical and research scenarios. For instance, the core definition may be applied, after adaptation, to the selection of candidates for epilepsy surgery or for referral to an epilepsy center for a comprehensive evaluation. Obviously, because presurgical evaluation and surgery

itself may entail risks, the decision to offer surgical treatment requires individual risk–benefit analysis that includes an assessment of possible success with additional trials of AEDs. The proposed definition also has implications for the design of randomized drug trials and should prove useful in the selection of patients for such trials, in which the criteria for considering a patient drug resistant are often poorly described. In this setting, a standard definition of drug resistance is important to ensure that results are comparable across trials. It would be particularly important to have clear documentation of previous AEDs that failed to control seizures, excluding those “uninformative” trials, and including the reasons for failure.

CONCLUSION

The development of the proposed consensus definition was driven by the growing need among medical practitioners and clinical researchers to adopt a common language in recognizing drug resistant epilepsy in the face of rapidly expanding therapeutic options. The definition aims to describe responsiveness to AED therapy but does not address the possible determining factors. Indeed, it is hoped that adoption of a common definition of drug resistance by researchers will facilitate the identification of such factors. During the process of formulating the definition, we were aware of deficiencies in the knowledge base, and inevitably assumptions were made that require testing and validation in future studies. In particular, there is a need for better documentation of the often fluctuating pattern of seizure occurrences and of the time course of treatment response in newly diagnosed patients. These data are required to provide a better understanding of the dynamic relationships among the various dimensions of treatment outcome. The proposed definition, therefore, is not intended to be prescriptive but represents a working framework. Clinicians and researchers should exercise their judgment in interpreting the principles described in this report when applying the definition to diverse settings. Some examples of how to apply the definition in various clinical scenarios are illustrated in Table 3. Because, as stated by Voltaire, the 18th century French Enlightenment writer and philosopher, “the perfect is the enemy of the good,” we hope that this consensus definition will serve its pragmatic purpose. Its adoption by the epilepsy community will allow future testing and refinement as and when new evidence emerges.

ACKNOWLEDGMENTS

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Disclosure: None of the authors has any conflict of interest to disclose.

GLOSSARY

Adverse effect	Any response to an intervention that is noxious and unintended, and which occurs when the intervention is applied with modalities normally used in humans for the therapy of a disease
Appropriate intervention	An intervention that has been shown to be safe and effective with appropriately documented evidence
Drug responsiveness	Whether the epilepsy is drug resistant, drug responsive, or neither (undefined)
Drug resistant epilepsy	Epilepsy in which seizures persist and seizure freedom is very unlikely to be attained with further manipulation of AED therapy. In the current proposal, it is defined as “failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”
Drug-responsive epilepsy	Epilepsy in which the patient receiving the current AED regimen has been seizure-free for a minimum of three times the longest preintervention interseizure interval or 12 months, whichever is longer
Intervention	A substance, device, or action applied to an epilepsy patient with the primary aim of reducing or preventing the occurrence of seizures
Seizure freedom	Freedom from all types of seizures for 12 months or three times the preintervention interseizure interval, whichever is longer
Treatment failure	The outcome whereby the patient did not attain seizure freedom after an informative trial of an intervention
Treatment outcome	Effect of an intervention as categorized by seizure control and occurrence of adverse effects
Undefined drug responsiveness	Drug responsiveness that cannot be classified as either drug responsive or drug resistant
Undetermined outcome	The situation whereby there is insufficient information to determine the outcome of an intervention in terms of seizure control or occurrence of adverse effects, or both
Uninformative trial	An intervention for which there is insufficient information to determine its outcome in an individual patient

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CMS Manual System	Department of Health & Human Services (DHHS)
Pub 100-03 Medicare National Coverage Determinations	Centers for Medicare & Medicaid Services (CMS)
Transmittal 10145	Date: May 22, 2020
	Change Request 11461

SUBJECT: National Coverage Determination (NCD) 160.18 Vagus Nerve Stimulation (VNS)

I. SUMMARY OF CHANGES: Effective for claims with dates of service on or after February 15, 2019, the Centers for Medicare & Medicaid Services covers Food and Drug Administration-approved vagus nerve stimulator devices for treatment-resistant depression through Coverage with Evidence Development when all reasonable and necessary criteria are met. This is National Coverage Determination 160.18, Vagus Nerve Stimulation.

The Federal government creates NCDs that are binding on the MACs who review and/or adjudicate claims, make coverage determinations, and/or payment decisions, and also binds quality improvement organizations, qualified independent contractors, the Medicare appeals council, and Administrative Law Judges (ALJs) (see 42 Code of Federal Regulations (CFR) section 405.1060(a)(4) (2005)). An NCD that expands coverage is also binding on a Medicare advantage organization. In addition, an ALJ may not review an NCD. (See section 1869(f)(1)(A)(i) of the Social Security Act.)

EFFECTIVE DATE: February 15, 2019

**Unless otherwise specified, the effective date is the date of service.*

IMPLEMENTATION DATE: June 23, 2020

Disclaimer for manual changes only: The revision date and transmittal number apply only to red italicized material. Any other material was previously published and remains unchanged. However, if this revision contains a table of contents, you will receive the new/revised information only, and not the entire table of contents.

II. CHANGES IN MANUAL INSTRUCTIONS: (N/A if manual is not updated)

R=REVISED, N=NEW, D=DELETED-Only One Per Row.

R/N/D	CHAPTER / SECTION / SUBSECTION / TITLE
R	1/160.18/Vagus Nerve Stimulation

III. FUNDING:

For Medicare Administrative Contractors (MACs):

The Medicare Administrative Contractor is hereby advised that this constitutes technical direction as defined in your contract. CMS does not construe this as a change to the MAC Statement of Work. The contractor is not obligated to incur costs in excess of the amounts allotted in your contract unless and until specifically authorized by the Contracting Officer. If the contractor considers anything provided, as described above, to be outside the current scope of work, the contractor shall withhold performance on the part(s) in question and immediately notify the Contracting Officer, in writing or by e-mail, and request formal directions regarding continued performance requirements.

Attachment - Business Requirements

Pub. 100-03	Transmittal: 10145	Date: May 22, 2020	Change Request: 11461
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SUBJECT: National Coverage Determination (NCD) 160.18 Vagus Nerve Stimulation (VNS)

EFFECTIVE DATE: February 15, 2019

**Unless otherwise specified, the effective date is the date of service.*

IMPLEMENTATION DATE: June 23, 2020

I. GENERAL INFORMATION

A. Background: Vagus nerve stimulation (VNS) is an example of neurostimulation therapy, which targets specific regions of the brain. VNS provides indirect modulation of brain activity through the stimulation of the vagus nerve. The implanted VNS system includes a pulse generator, which is surgically inserted underneath the skin of the chest. For treatment of treatment resistant depression (TRD), it is subcutaneously connected to an electrode attached to the left vagus nerve in the neck.

Section 160.18 of the Medicare National Coverage Determinations (NCD) Manual establishes conditions of coverage for VNS. In 1999, the Centers for Medicare & Medicaid Services (CMS) issued an NCD to provide coverage for VNS for patients with medically refractory partial onset seizures, for whom surgery is not recommended or for whom surgery has failed. On May 4, 2007, CMS determined that there was sufficient evidence to conclude that VNS was not reasonable and necessary for TRD and it has remained non-covered since then.

B. Policy: The scope of this reconsideration is limited to VNS for TRD. Effective for claims with dates of service on or after February 15, 2019, CMS will cover Food and Drug Administration-approved VNS devices for TRD through Coverage with Evidence Development (CED) when offered in a CMS-approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least one year 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.

Each study must be approved by CMS and as a fully-described, written part of its protocol, must address whether VNS improves health outcomes for TRD patients compared to a control group, by answering all of the research questions included in the coverage criteria.

There is also criteria that must be used to identify patients demonstrating TRD.

Individuals who receive placebo VNS will be offered active VNS at the end of the trial.

VNS is non-covered for the treatment of TRD when furnished outside of a CMS-approved CED study.

All other indications of VNS for the treatment of depression are nationally non-covered.

Patients previously implanted with a VNS device for TRD may receive a VNS device replacement if it is required due to the end-of-battery life, or any other device-related malfunction. These patients do not require either ICD-10 diagnosis codes or CED-related coding. These claims WILL require the –KX modifier attesting to the reasonable and necessary need for the replacement device based off NCD160.18 criteria.

NOTE: VNS for medically refractory seizures and hypoglossal nerves continue to be processed as they are currently.

NOTE: A subsequent Change Request will be issued shortly that will provide updates to the Pub. 100-04 Claims Processing Manual and instructions for processing claims through the CMS shared systems in regard to VNS for TRD.

II. BUSINESS REQUIREMENTS TABLE

"Shall" denotes a mandatory requirement, and "should" denotes an optional requirement.

Number	Requirement	Responsibility							
		A/B MAC		D M E	Shared-System Maintainers				Other
		A	B		H H H	M A C	F I S S	M C S	
11461.1	Effective February 15, 2019, contractors shall cover VNS for TRD for patients that meet the specific coverage indications and criteria described at Pub. 100-03, NCD Manual, section 160.18.	X	X						
11461.2	A/B MACs shall work together collaboratively to ensure consistent national editing across jurisdictions.	X	X						
11461.2.1	Contractors shall attend up to 3 1-hour calls to discuss feedback regarding implementation of coding for this policy in a subsequent Change Request, and how to ensure consistent national editing across MACS locally. Contractors shall provide appropriate points-of-contact for staffing the meetings and send the contact information within 7 business days of the date of issuance of this CR to:David.Dolan@cms.hhs.gov. NOTE: CMS shall schedule the calls at a later date.	X	X						
11461.3	A/B MACs shall implement local edits in each respective jurisdiction until such time as CMS may determine shared edits to be appropriate. A subsequent CR transferring some of this editing to the shared systems is forthcoming shortly.	X	X						

III. PROVIDER EDUCATION TABLE

Number	Requirement	Responsibility					
		A/B MAC			D M E	C E D I	
		A	B	H H H			M A C
11461.4	MLN Article: CMS will make available an MLN Matters provider education article that will be marketed through the MLN Connects weekly newsletter	X	X				

Number	Requirement	Responsibility				
		A/B MAC			D M E M A C	C E D I
		A	B	H H H		
	shortly after the CR is released. MACs shall follow IOM Pub. No. 100-09 Chapter 6, Section 50.2.4.1, instructions for distributing MLN Connects information to providers, posting the article or a direct link to the article on your website, and including the article or a direct link to the article in your bulletin or newsletter. You may supplement MLN Matters articles with localized information benefiting your provider community in billing and administering the Medicare program correctly. Subscribe to the “MLN Matters” listserv to get article release notifications, or review them in the MLN Connects weekly newsletter.					

IV. SUPPORTING INFORMATION

Section A: Recommendations and supporting information associated with listed requirements: N/A

"Should" denotes a recommendation.

X-Ref Requirement Number	Recommendations or other supporting information:

Section B: All other recommendations and supporting information: N/A

V. CONTACTS

Pre-Implementation Contact(s): David Dolan, 410-786-3365 or David.Dolan@cms.hhs.gov (Coverage and Analysis)

Post-Implementation Contact(s): Contact your Contracting Officer's Representative (COR).

VI. FUNDING

Section A: For Medicare Administrative Contractors (MACs):

The Medicare Administrative Contractor is hereby advised that this constitutes technical direction as defined in your contract. CMS does not construe this as a change to the MAC Statement of Work. The contractor is not obligated to incur costs in excess of the amounts allotted in your contract unless and until specifically authorized by the Contracting Officer. If the contractor considers anything provided, as described above, to be outside the current scope of work, the contractor shall withhold performance on the part(s) in question and immediately notify the Contracting Officer, in writing or by e-mail, and request formal directions regarding continued performance requirements.

ATTACHMENTS: 0

160.18- Vagus Nerve Stimulation (VNS)

(Rev. 10145; Issued: 05-22-2020; Effective: 02-19-2019; Implementation: 06-23-2020)

A. General

Vagus Nerve Stimulation (VNS) is a pulse generator, similar to a pacemaker, that is surgically implanted under the skin of the left chest and an electrical lead (wire) is connected from the generator to the left vagus nerve. Electrical signals are sent from the battery-powered generator to the vagus nerve via the lead. These signals are in turn sent to the brain. The Food and Drug Administration (FDA) approved VNS for treatment of refractory epilepsy in 1997 and for resistant depression in 2005.

B. Nationally Covered Indications

Effective for services performed on or after July 1, 1999, 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.

Effective for services performed on or after February 15, 2019, the Centers for Medicare & Medicaid Services (CMS) will cover FDA-approved VNS devices for treatment resistant depression (TRD) through Coverage with Evidence Development (CED) when offered in a CMS-approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least one year 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.

Each study must be approved by CMS and as a fully-described, written part of its protocol, must address whether VNS improves health outcomes for TRD patients compared to a control group, by answering all of the following research questions below. The details of the prospective longitudinal study must be described in the original protocol for the double-blind, randomized, placebo-controlled trial. Response is defined as a $\geq 50\%$ improvement in depressive symptoms from baseline, as measured by a guideline recommended depression scale assessment tool. Remission is defined as being below the threshold on a guideline recommended depression scale assessment tool. The following research questions must be addressed in a separate analysis for patients with bipolar and unipolar disease.

Research Questions:

- What is the rate of response (defined as person months of response/total months of study participation)?*
- What is the rate of remission (defined as person months of response/total months of study participation)?*
- What is the time from treatment until response scores are first achieved?*
- What is the time from treatment until remission scores are first achieved?*
- What are the population distributions of the maximum months of response, both consecutive and overall, separately?*
- What are the population distributions of the maximum months of remission, both consecutive and overall, separately?*
- What are the patient variables associated with successful treatment of TRD with VNS?*
- What are the observed harms?*
- What are the changes in disability, quality of life, general psychiatric status, and suicidality?*

Patient Criteria:

The following criteria must be used to identify patients demonstrating TRD:

- *The patient must be in a major depressive disorder (MDD) episode for \geq two years or have had at least four episodes of MDD, including the current episode. In order to confirm the patient has MDD, accepted diagnostic criteria from the most current edition of the Diagnostic and Statistical Manual for Mental Disorder (DSM) and a structured clinical assessment are to be used.*
- *The patient's depressive illness meets a minimum criterion of four prior failed treatments of adequate dose and duration as measured by a tool designed for this purpose.*
- *The patient is experiencing a major depressive episode (MDE) as measured by a guideline recommended depression scale assessment tool on two visits, within a 45-day span prior to implantation of the VNS device.*

Patients must maintain a stable medication regimen for at least four weeks before device implantation.

If patients with bipolar disorder are included, the condition must be carefully characterized.

Patients must not have:

- *Current or lifetime history of psychotic features in any MDE;*
- *Current or lifetime history of schizophrenia or schizoaffective disorder;*
- *Current or lifetime history of any other psychotic disorder;*
- *Current or lifetime history of rapid cycling bipolar disorder;*
- *Current secondary diagnosis of delirium, dementia, amnesia, or other cognitive disorder;*
- *Current suicidal intent; or,*
- *Treatment with another investigational device or investigational drugs.*

Individuals who receive placebo VNS will be offered active VNS at the end of the trial.

In addition, CMS will review studies to determine if they meet the 13 criteria listed below. If CMS determines that they meet these criteria, the study will be posted on CMS' CED website

(<https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/index.html>).

- The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.*
- The rationale for the study is well supported by available scientific and medical evidence.*
- The study results are not anticipated to unjustifiably duplicate existing knowledge.*
- The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.*
- The study is sponsored by an organization or individual capable of completing it successfully.*
- The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.*
- All aspects of the study are conducted according to appropriate standards of scientific integrity.*
- The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.*
- The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.*
- The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).*

- k) *The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessible manner; either in a peer-reviewed scientific journal (in print or online), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).*
- l) *The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.*
- m) *The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.*

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The principal investigator must submit the complete study protocol, identify the relevant CMS research questions that will be addressed and cite the location of the detailed analysis plan for those questions in the protocol, plus provide a statement addressing how the study satisfies each of the standards of scientific integrity (a. through m. listed above), as well as the investigator's contact information, to the address below. The information will be reviewed, and approved studies will be identified on the CMS website.

*Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services (CMS)
7500 Security Blvd., Mail Stop S3-02-01
Baltimore, MD 21244-1850*

C. Nationally Non-Covered Indications

Effective for services performed on or after July 1, 1999, 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.

VNS is non-covered for the treatment of TRD when furnished outside of a CMS-approved CED study.

All other indications of VNS for the treatment of depression are nationally non-covered.

D. Other

Patients implanted with a VNS device for TRD may receive a VNS device replacement if it is required due to the end of battery life, or any other device-related malfunction.


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RESEARCH

Open Access



The effects of vagus nerve stimulation on the course and outcomes of patients with bipolar disorder in a treatment-resistant depressive episode: a 5-year prospective registry

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Abstract

Background: To compare illness characteristics, treatment history, response and durability, and suicidality scores over a 5-year period in patients with treatment-resistant bipolar depression participating in a prospective, multicenter, open-label registry and receiving Vagus Nerve Stimulation Therapy (VNS Therapy) plus treatment-as-usual (VNS + TAU) or TAU alone.

Methods: Response was defined as $\geq 50\%$ decrease from baseline Montgomery–Åsberg Depression Rating Scale (MADRS) total score at 3, 6, 9, or 12 months post-baseline. Response was retained while MADRS score remained $\geq 40\%$ lower than baseline. Time-to-events was estimated using Kaplan–Meier (KM) analysis and compared using log-rank test. Suicidality was assessed using the MADRS Item 10 score.

Results: At baseline (entry into registry), the VNS + TAU group ($N = 97$) had more episodes of depression, psychiatric hospitalizations, lifetime suicide attempts and higher suicidality score, more severe symptoms (based on MADRS and other scales), and higher rate of prior electroconvulsive therapy than TAU group ($N = 59$). Lifetime use of medications was similar between the groups (a mean of 9) and was consistent with the severe treatment-resistant nature of their depression. Over 5 years, 63% (61/97) in VNS + TAU had an initial response compared with 39% (23/59) in TAU. The time-to-initial response was significantly quicker for VNS + TAU than for TAU ($p < 0.03$). Among responders in the first year after implant, the KM estimate of the median time-to-relapse from initial response was 15.2 vs 7.6 months for VNS + TAU compared with TAU (difference was not statistically significant). The mean reduction in suicidality score across the study visits was significantly greater in the VNS + TAU than in the TAU group ($p < 0.001$).

Conclusions: The patients who received VNS + TAU included in this analysis had severe bipolar depression that had proved extremely difficult to treat. The TAU comparator group were similar though had slightly less severe illnesses on some measures and had less history of suicide attempts. Treatment with VNS + TAU was associated with a higher likelihood of attaining a response compared to TAU alone. VNS + TAU was also associated with a significantly greater mean reduction in suicidality.

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Limitations: In this registry study, participants were not randomized to the study treatment group, VNS Therapy stimulation parameters were not controlled, and there was a high attrition rate over 5 years.

Trial registration ClinicalTrials.gov NCT00320372. Registered 3 May 2006, <https://clinicaltrials.gov/ct2/show/NCT00320372> (retrospectively registered)

Keywords: Bipolar disorder, Depression, Vagus Nerve Stimulation Therapy, VNS TRD registry, Response, Suicidality, Treatment-resistant depression

Background

Patients with bipolar disorder are symptomatic about 50% of the time, the vast majority of which is depression (Judd et al. 2002, 2003). However, treatment options for bipolar depression are limited. For example, the UK National Institute for Health and Social Care (NICE) guidelines for the management of bipolar depression list just 3 treatments that are supported by replicated randomized controlled trials: lamotrigine, quetiapine, and olanzapine (with or without fluoxetine) (National Institute for Health and Care Excellence 2014). Since publication of the NICE guidelines, additional evidence has emerged from randomized controlled trials supporting the efficacy of lurasidone for the acute treatment of bipolar depression (Loebel et al. 2014a, b). This limited number of treatment options for bipolar depression is further compromised as quetiapine and olanzapine are often poorly tolerated due to weight gain and sedation (Calabrese et al. 2005; Tohen et al. 2003).

The clinical challenge of managing bipolar depression is further illustrated by observations of high rates of antidepressant usage (Kessing et al. 2016; Yoon et al. 2018) despite evidence of questionable efficacy (National Institute for Health and Care Excellence 2014; Sidor and Macqueen 2011). The implication is that many patients suffer from treatment-resistant bipolar depression (TRBD). The prevalence of TRBD is unknown due to a lack of a consensus definition (Hidalgo-Mazzei et al. 2019). However, it is known that about 50% and 30% of depressed bipolar patients remain depressed at 6 and 12 months, respectively, following initiation of antidepressant treatment; and the lack of treatment effects is due to non-response, intolerance, or non-acceptance of treatment (Kupfer et al. 2000). As a result, TRBD is the major contributor to the enormous burden of disease associated with bipolar disorder (Ferrari et al. 2016).

Given the significant unmet need with regards to the management of bipolar depression, it is important that alternative treatment options for patients with TRBD are explored. One potential option is Vagus Nerve Stimulation Therapy (VNS Therapy).

VNS Therapy has primarily been examined in unipolar treatment-resistant depression (TRD). The largest data set supporting its use in TRD is a 5-year VNS TRD

registry of nearly 500 participants (representing both unipolar and bipolar TRD) who received adjunctive VNS Therapy plus treatment-as-usual (VNS + TAU). In this registry, the VNS-implanted TRD participants were compared with 300 other TRD participants with similar clinical presentations who received only TAU (Aaronson et al. 2017). It is important to note that the participants included in the registry were not randomized to VNS + TAU or TAU. Rather, treatment was determined by a participant's choice and availability of VNS Therapy.

The data from the VNS TRD registry revealed that the adjunctive VNS Therapy group had significantly higher 5-year cumulative response (67.6% vs 40.9%) and remission (43.3% vs 25.7%) rates compared to the TRD patients who received TAU alone (Aaronson et al. 2017). Additionally, VNS + TAU led to a more durable response as the time-to-relapse from initial response for responders in the first year was 10.1 months versus 7.3 months for participants receiving TAU alone (Kumar et al. 2019). Safety assessment in the registry also found a greater reduction in suicidality in participants receiving VNS + TAU compared to TAU alone (Aaronson et al. 2017).

Nierenberg and colleagues have previously described the outcomes of 25 patients with TRBD who were included in acute and long-term early studies of VNS Therapy for the treatment of depression (Nierenberg et al. 2008). The authors reported that the antidepressant efficacy outcomes for these TRBD patients were similar to the unipolar TRD patients.

Benefit of VNS Therapy in patients with bipolar disorder is also supported by a published case series that included 5 patients who demonstrated sustained improvement in depressive symptoms and a lack of manic episodes during the follow-up period; and 3 of these patients were followed for about 5 years (Oldani et al. 2015).

In this report—using the 5-year VNS TRD registry discussed above—we examine the pre-treatment clinical characteristics and the clinical outcomes in a subgroup of TRD patients with TRBD comparing VNS + TAU versus TAU alone based on the following areas of interest:

- I. Illness characteristics and previous treatments received prior to inclusion in the registry
- II. Cumulative depressive symptom response (defined by $\geq 50\%$ reduction in Montgomery–Åsberg Depression Rating Scale [MADRS]) over the 5-year registry observation period
- III. Duration of response (defined a priori as maintenance of $\geq 40\%$ reduction from baseline MADRS)
- IV. Change in suicidality score over the 5-year registry observation period

Methods

Study population

Analysis of the 5-year VNS TRD registry data set described here included 156 participants with bipolar disorder (both bipolar I and II disorders): $n=97$ received VNS+TAU and $n=59$ received TAU. To be eligible to participate in the VNS TRD Registry, participants had to be over 18 years of age, experiencing an active major depressive episode of 2 years or longer in duration (either unipolar or bipolar), or had a history of at least 3 major depressive episodes, including the current depressive episode, and a history of inadequate response to 4 or more adequate antidepressant treatments (dosage per Physicians' Desk Reference labeling for a minimum of 4 weeks), which could include electroconvulsive therapy (ECT). Participants could not have a history of a psychotic disorder or rapid-cycling bipolar disorder, or psychotic features in the present major depressive episode. A more detailed list of study entry criteria can be found elsewhere (Aaronson et al. 2017; Olin et al. 2012). ClinicalTrials.gov Identifier: NCT00320372.

Study treatment

Before enrollment into the VNS TRD Registry, participants could select the treatment group of their choice (ie, TAU or VNS+TAU). The exception to this were those VNS+TAU subjects who entered the registry via rollover from a previous flexible dose-finding VNS trial (Aaronson et al. 2013). Some participants could be assigned to receive the alternate treatment by the site for various reasons, including availability of surgical implantation at a site, number of allocated slots for implantation, or failure to qualify for insurance reimbursement or VNS Therapy implantation. Device implantation surgery and related medical care were covered either by a participant's insurance policy or from personal funds.

Assessments

The assessment of the registry participants included in this analysis has been detailed elsewhere (Aaronson et al. 2017). Participants in the VNS+TAU group underwent

implantation during Visit 2 (baseline). Post-baseline follow-up visits for all participants were conducted at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months. The primary measure of depression for this registry was the MADRS (Carmody et al. 2006) which was administered by central blinded raters. Other psychiatric outcome measures were the Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR) (Trivedi et al. 2004; Rush et al. 2003) and the Clinical Global Impression (CGI) scale (Guy 1976).

Statistical analysis

The intent-to-treat (ITT) population included 195 registry participants with bipolar disorder ($n=134$ VNS+TAU; $n=61$ TAU) defined as those who completed their baseline visit, received their respective treatment, and completed at least one post-baseline assessment. To ensure consistent VNS Therapy dose and follow-up schedule, the analysis sample excluded individuals who were "crossed over" from VNS Therapy treatment in the previously reported flexible dose study ($n=37$) since most of these participants had consistent follow-up data for only 1 year (Aaronson et al. 2013). In addition, we excluded participants who had a baseline MADRS score <10 indicating that they were already remitted from their major depressive episode (Zimmerman et al. 2004); this excluded $n=2$ from the TAU group. The remaining 156 TRBD patients comprised of $N=97$ receiving VNS+TAU and $N=59$ receiving TAU and were included in the analysis described here. Note that participants who were crossed over to another treatment group during the study were censored at the last visit before cross-over.

Time-to-initial response was defined as the time from baseline to the first visit when there was reduction in MADRS score of $\geq 50\%$ compared to baseline. A probability of time-to-initial response was estimated using Kaplan–Meier (KM) method. KM probability estimates were calculated for the time-to-event with 95% confidence intervals at 3, 6, 9, and 12 months. Time-to-event curves for the 2 treatment groups were compared using Log-rank test. A Cox proportional-hazard model was used to estimate the hazard ratio (and 95% confidence interval) of the instantaneous chance of a participant having an event in the VNS+TAU group compared to the TAU group at any given time during follow-up.

Given the different proportion of participants with bipolar I or II disorder between the VNS+TAU and TAU groups, a second Cox proportional-hazard model was used to evaluate the time-to-first response, adjusting for the effects of bipolar diagnosis and interaction between treatment and bipolar diagnosis.

Persistence of response was defined as an ongoing reduction in MADRS score of $\geq 40\%$ after an

antidepressant response was recorded (reduction of baseline MADRS of $\geq 50\%$). Persistence of response was calculated for all study participants who had an initial response in the first year of study treatment. Participants were categorized in subgroups by the visit when the initial response occurred. A KM analysis was performed to compare the retention of response in VNS+TAU and TAU alone in a time-to-event analysis framework.

Participants were considered severely suicidal if they had a score of ≥ 4 on MADRS Item 10. The percentage who were still severely suicidal was calculated for each post-baseline visit. Similarly, the percentage who were non-severely suicidal at baseline who became severely suicidal was calculated for each post-baseline visit. Average change in suicidality score for VNS+TAU and TAU on MADRS Item 10 is presented for each post-baseline visit.

If there were 1 or 2 consecutive missing data, then the data was imputed with the average of the 2 adjacent non-missing data. No imputation was done for 3 or more consecutive missing data points. After imputation, participants were censored at the last visit with non-missing data for all the analysis. Thus, there were a total of 412 visits with data for TAU group and 856 visits with data for VNS+TAU group in the censored data set. Imputation for a single missed data point in the censored data set was done for 32 visits (32/412 [7.8%]) of the available data for TAU group and for 59 visits (59/856 [6.9%]) of the available data for VNS+TAU group. Imputation for 2 consecutive missing data points was done for 14 visits (14/412 [3.4%]) of the available data for TAU group and for 28 visits (28/856 [3.3%]) of the available data for VNS+TAU group. Overall, there were 46 imputed data (46/412 [11.2%]) of available data in TAU group and 87 imputed data (87/856 [10.2%]) of all available data in VNS+TAU group.

This imputation method has desirable properties as detailed in Kumar et al. (2019). The data set has a regular response pattern (when defined as reduction of MADRS score of $\geq 50\%$), ie, the same response at the adjacent visits around one missing data: 78.1% for TAU and 62.7% for VNS+TAU, and around 2 consecutive missing data items: 100% for TAU and 78.1% for VNS+TAU. Thus, occurrence of initial or second response could have been altered due to imputation only for 1.7% of the censored data for the TAU group and 3.3% of censored data in the VNS+TAU group. Similarly, the censored data set provided a regular response pattern (when defined as reduction of MADRS score of $\geq 40\%$) around 1 missing data: 71.9% for TAU and 57.6% for VNS+TAU and around 2 consecutive missing data: 100% for TAU and 78.6% for VNS+TAU. Thus, prolongation of the response maintenance could have occurred in only 2.2% of the censored

data in the TAU group and 3.6% of the censored data in the VNS+TAU group. Given this small percentage of data that could have an altered response pattern due to imputation, it was concluded that the imputation method would work well for this data set and that it could not have altered the result substantially in favor of any treatment group.

Results

Sample demographics and illness characteristics

Table 1 summarizes demographic information and baseline clinical characteristics for the analysis sample.

The age at onset of depressive symptoms (around 19–20 years of age) and age at initial diagnosis of an episode of depression (around 8 years later) were similar between the groups. Overall, there were significantly higher proportion of participants with a bipolar I diagnosis in the VNS+TAU group ($n=65$ [67.0%] vs $n=28$ [47.5%]) and lower rate of those with a bipolar II diagnosis (32 [33.0%] vs 31 [52.5%]) compared with the TAU group (Chi-squared test for homogeneity, $p=0.0158$). The VNS+TAU group had experienced more episodes of lifetime depressive episodes than the TAU group, though this was not statistically significant. Moreover, the VNS+TAU group had a history of more psychiatric hospitalizations within the 5 years prior to entering the registry and had more lifetime suicide attempts. Further, the VNS+TAU subjects had greater depressive symptomatology as assessed by the MADRS, QIDS-SR, and CGI. Additionally, the VNS+TAU group scored significantly higher on the suicidality item of the MADRS Item 10.

Treatment histories are presented in Table 2. There was a very similar distribution of lifetime use of medications. The mean number of lifetime antidepressant treatment courses was approximately 9, with a maximum of 14 in both treatment groups. All study participants had received antidepressants in the past or present, and selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) were the most frequently prescribed antidepressant medication classes. With regard to medications specifically recommended in guidelines for bipolar depression (National Institute for Health and Care Excellence 2014), lamotrigine was the drug most commonly prescribed, followed by quetiapine. About half of the VNS+TAU group had taken lithium or sodium valproate, slightly more than seen in the TAU group. Just over half of the VNS+TAU group had prior ECT treatment, with a smaller number in the TAU group (54% vs 39%). Most participants had received psychological therapies, with a lifetime frequency of individual therapy being above 80% in both groups.

Table 1 Demographic and baseline clinical characteristics

	VNS + TAU (N = 97)	TAU (N = 59)	P *
Mean age ± SD (years)	47.0 ± 10.2	47.8 ± 10.6	0.65
Female, n (%)	72 (74.2%)	47 (79.7%)	0.56
White, n (%)	93 (95.9%)	56 (94.9%)	1
Mean age ± SD at initial onset of depressive symptoms (years)	20.0 ± 11.5	18.9 ± 9.2	0.51
Mean age ± SD at initial diagnosis of depression (years)	26.9 ± 10.6	27.9 ± 11.6	0.59
Lifetime number of diagnosed depressive episode	20.7 ± 29.2	13.7 ± 23.2	0.10
Psychiatric hospitalizations within the 5 years prior to registry enrollment	3.6 ± 5.4	1.5 ± 2.1	< 0.001
Lifetime suicide attempts	2.7 ± 4.8	1.5 ± 2.9	0.05
DSM-IV-TR primary diagnosis, n (%)			
Bipolar I disorder, currently moderately severe major depressive episode	19 (19.6%)	18 (30.6%)	0.17
Bipolar I disorder, currently severe major depressive episode	46 (47.4%)	10 (16.9%)	< 0.001
Bipolar II disorder, currently depressed	32 (33.0%)	31 (52.5%)	0.025
Baseline scores, n (%)			
Montgomery–Åsberg Depression Rating Scale	33.7 ± 7.3	29.7 ± 5.9	< 0.001
Clinical Global Impression—Severity	5.2 ± 0.8	4.7 ± 0.7	< 0.001
Quick Inventory of Depressive Symptomatology-Self Report	18.4 ± 4.9	15.9 ± 5.2	0.004
Suicidality-based on MADRS Item 10	2.7 ± 1.4	2.0 ± 1.2	0.003

SD standard deviation

* P-values are from two-sided t-test for comparing means assuming unequal variance or z-test for comparing proportions

Table 2 Lifetime treatment histories

	VNS + TAU (N = 97)	TAU (N = 59)
Number of treatment courses*		
Mean	9.2	9.0
Maximum	14	14
Minimum	3	4
Antidepressants, n (%)	97 (100%)	59 (100%)
Bupropion	71 (73%)	38 (64%)
Selective serotonin reuptake inhibitors (SSRIs)	88 (91%)	50 (85%)
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	78 (80%)	48 (81%)
Other	68 (70%)	35 (59%)
Antipsychotics, anticonvulsants, and other medications, n (%)		
Lamotrigine	62 (64%)	44 (75%)
Quetiapine	56 (58%)	35 (59%)
Olanzapine	37 (38%)	24 (24%)
Olanzapine + fluoxetine	5 (5%)	6 (10%)
Lithium	53 (55%)	25 (42%)
Sodium valproate	54 (56%)	20 (34%)
Electroconvulsive therapy, n (%)	53 (54%)	23 (39%)
Psychological therapies, n (%)		
Cognitive behavioral therapy (CBT)	44 (45%)	23 (39%)
Individual therapy	83 (86%)	48 (81%)

* A course of treatment was defined as at least a 4-week continuous period in which a patient used one or more treatments for their depression. A new course of treatment started each time a drug was added or dropped. Courses of treatment were classified as electroconvulsive therapy, monotherapy, combination therapies, augmentation therapies, or other psychiatric treatments

Cumulative response rates

Over the 5-year observation period, 61 of 97 (63%) in the VNS+TAU group had an initial response (defined as $\geq 50\%$ reduction in MADRS from baseline) compared to 23 of 59 (39%) of participants in the TAU group. The KM plot in Fig. 1 shows that time-to-initial response was significantly shorter for VNS+TAU than for TAU alone ($p=0.03$ for log-rank test). The estimated cumulative probability for the time-to-initial response was higher for the VNS+TAU group as compared to the TAU group over most of the follow-up period. Median time-to-initial response was 13.7 month (Q1=5, Q3=37.7) for VNS+TAU group compared to 42.1 months (Q1=8.3, Q3=not estimable) for TAU group. Hazard ratio for time-to-initial response for VNS+TAU compared to TAU was 1.7 (95% CI 1, 2.7) meaning a larger chance for a participant in the VNS+TAU group to get an initial response compared to a participant in the TAU group at any given time during the follow-up, though the hazard ratio was not statistically significant.

The Cox proportional-hazard model on time-to-first response adjusting for the effects of bipolar diagnosis and the correspondent interaction, confirmed the benefit of VNS+TAU in reducing the time-to-first response (HR=1.6; 95% CI 0.98, 2.7) and VNS+TAU showed trends of effectiveness in both sub-populations (HR=2.1 in bipolar I and HR=1.3 in bipolar II, even if a significant treatment effect of VNS+TAU vs TAU was seen just in the participants with bipolar I (95% CI 1.0, 4.3) (Table 3). This may in part be driven by the smaller number of patients with bipolar II vs bipolar I disorder ($n=59$ vs $n=97$) and the low rate of responses in the bipolar II subgroup ($n=17$ vs $n=14$ for the VNS+TAU and TAU groups, respectively). Due to the low rate, it was also not possible to estimate the 95% confidence intervals in KM analysis for the median time-to-first response in the bipolar II patients (Table 4).

Duration of response

Maintenance of response was defined a priori as maintenance of $\geq 40\%$ reduction from baseline MADRS

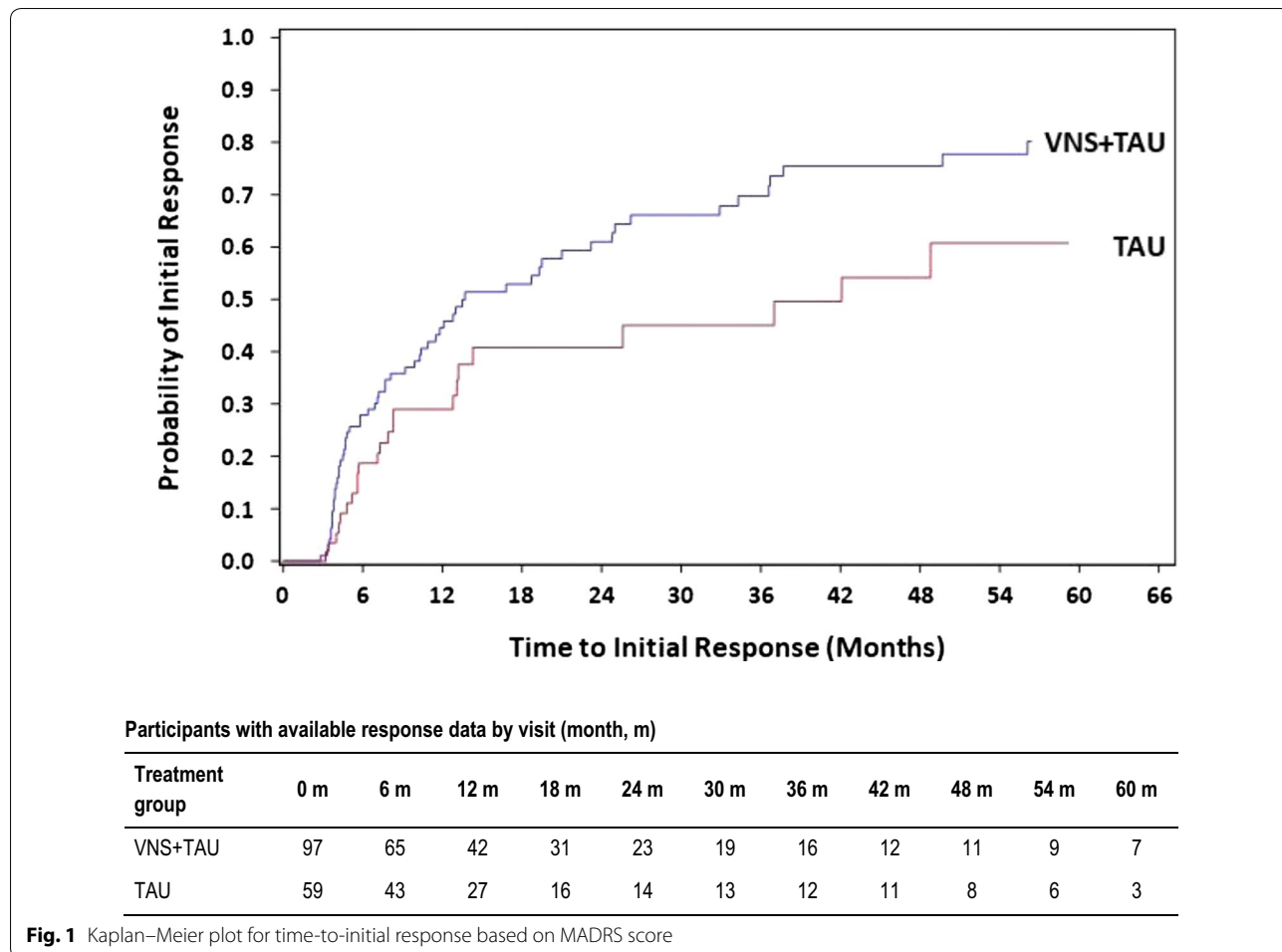


Table 3 Cox proportional-hazards model examining effect of bipolar diagnosis on the time-to-first response

Effect	Hazard ratio	95% CI lower limit	95% CI upper limit	p-value
VNS + TAU vs TAU	1.6	0.98	2.7	0.06
Bipolar II vs bipolar I	0.96	0.6	1.6	0.9
VNS vs TAU in bipolar I	2.1	1.0	4.3	0.04
VNS vs TAU in bipolar II	1.3	0.6	2.6	0.5

and assessed in those who showed a response in the first year of follow-up. In the VNS + TAU group, 46 of the 61 responders (75.4%) responded in the first year; and in the TAU group, 19 of the 23 responders (82.6%) responded in the first year. Numbers are small and hence comparisons between the 2 groups may not be robust.

A KM analysis of the data estimated that the median time-to-relapse from initial response in the first year was 15.2 months (Q1 = 6.7, Q3 = 25.4) for the VNS + TAU group compared with 7.6 months (Q1 = 3.4, Q3 = 14.7) for the TAU group. The hazard ratio for relapse after the initial response was 0.7 (95% CI 0.3, 1.4) in favor of VNS, though this was not statistically significant. In terms of actual data, it was possible to examine maintenance of response 6 months after initial response in participants who demonstrated an initial response at the 3-, 6-, or 12-month study visits. Of these, 30/39 (76.9%) in the VNS + TAU group were maintaining a response 6 months later, compared with 10/18 (55.6%) in the TAU group. There was limited data to examine maintenance of response 12 months after initial response since this was only available for those who showed an initial response at the 6- or 12-month visits. However, again, the proportion maintaining a response was numerically higher in the VNS + TAU compared with TAU group (6/13 [46.1%] vs 3/11 [27.3%], respectively).

Table 4 Kaplan–Meier estimates for time-to-first response, months

	First quartile (95% CI)	Median (95% CI)	Third quartile (95% CI)
Bipolar 1			
VNS + TAU	5.8 (4.1, 7.7)	13 (7.7, 23.2)	36.6 (23.2, NE)
TAU	13.1 (4, 37)	37 (13.1, NE)	NE (37, NE)
Bipolar 2			
VNS + TAU	4.7 (3.7, 10.4)	19.5 (9.2, NE)	NE (24.8, NE)
TAU	7.9 (4.3, 13.2)	14.3 (8.3, NE)	NE (48.8, NE)

CI confidence interval, NE not estimable

Suicidality

A total of 33 (33/97; 34%) in the VNS + TAU group and 8 (8/59; 14%) in the TAU group were severely suicidal at baseline based on MADRS (a score ≥ 4 on MADRS Item 10 corresponding to the responses “probably better off dead” and “active preparations for suicide”). Notably, the mean reduction in suicidality score across the study visits was significantly greater in the VNS + TAU than in the TAU group ($P < 0.001$ as per F-test) (Fig. 2).

In each treatment group, the percentage who became severely suicidal post-baseline was less than 15% (Table 5) and the difference between the treatment groups was not statistically significant.

Discussion

Given the frequency of TRBD and its impact on patients with bipolar disorder, it is important to consider all possible treatment options. This post-hoc analysis suggests that in a non-randomized study following the outcomes of patients with TRBD for up to 5 years, the addition of VNS Therapy to TAU had significantly greater cumulative response rates, faster onset of antidepressant response, and the responses were longer in duration than in participants receiving TAU alone. Critically, VNS + TAU was also associated with a significantly greater reduction in suicidal ideation compared with TAU alone, despite the VNS + TAU group being more severely depressed at baseline and with high ratings of suicidality. These findings are consistent with the observations made in a much larger group of patients with unipolar or bipolar depression (Aaronson et al. 2017). They are also consistent with a previous post-hoc analysis of 25 patients with TRBD who made up 11% of a larger TRD population who received VNS Therapy alongside TAU in a sham-controlled acute study with long-term open-label follow-up (Nierenberg et al. 2008). The only other study of the safety and efficacy of VNS Therapy in bipolar disorder is a 1-year pilot study of VNS Therapy in 9 patients with rapid cycling bipolar disorder that did not have a comparator group (Marangell et al. 2008).

These findings suggest that VNS Therapy may be effective in patients with very significant difficult to treat

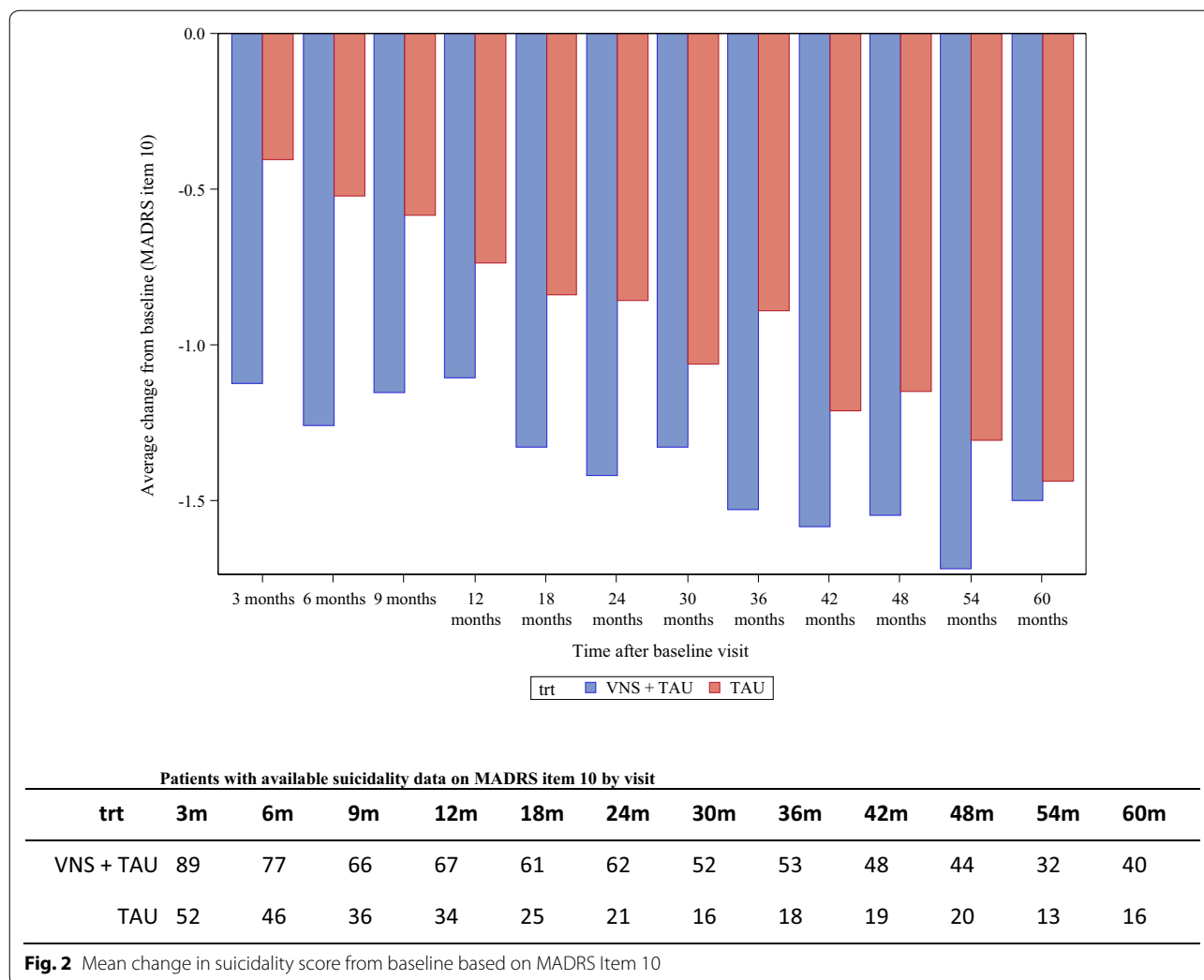


Fig. 2 Mean change in suicidality score from baseline based on MADRS Item 10

depression in the context of bipolar disorder. Those treated with VNS Therapy had an average of 20.7 lifetime episodes of depression, 3.6 psychiatric hospitalizations in the previous 5 years, and 2.7 lifetime suicide attempts. They had received an average of 9 medication treatment courses over their lifetime and all had received an antidepressant, despite the lack of evidence that these are efficacious in patients with bipolar disorder (Sidor and Macqueen 2011; Young et al. 2010). The vast majority had also received psychotherapy, and about half (54%) had been treated with ECT. Importantly, despite the VNS+TAU participants having considerably more severe depressive histories (statistically significantly more severe depressive symptomology and greater suicidal ideation at baseline prior to treatment), the VNS+TAU group demonstrated superior antidepressant outcomes.

The magnitude of the effect on cumulative response rates with VNS+TAU versus TAU was slightly larger than that seen in patients with unipolar depression in

the original analysis of this data set (Aaronson et al. 2017). However, the assessment of the impact of VNS Therapy on durability of response in this current analysis is not as great as that seen in the unipolar patients studied as part of this registry (Kumar et al. 2019). This is perhaps not surprising given that bipolar disorder is more recurrent than unipolar disorder (Angst et al. 2003). While there was no significant difference in durability of response between the VNS+TAU and TAU groups in this analysis, numerically the participants receiving VNS+TAU did better. The lack of significant findings with regards to durability of response may have in part arisen due to the small numbers of patients included in the analysis, particularly at later visit time points, and the relative infrequency of assessment of mood symptoms. Given the importance of prophylaxis in a recurrent disorder such as bipolar disorder, further research investigating the prophylactic efficacy of VNS Therapy is indicated, including in

Table 5 Change in suicidal rating from non-severe to severe based on MADRS Item 10

Visit months	VNS + TAU	TAU
3	3/57 (5.3%)	3/44 (6.8%)
6	2/49 (4.1%)	4/40 (10%)
9	1/43 (2.3%)	2/32 (6.3%)
12	6/44 (13.6%)	2/28 (7.1%)
18	1/39 (2.6%)	1/22 (4.5%)
24	0/36 (0%)	0/19 (0%)
30	1/29 (3.4%)	0/14 (0%)
36	1/30 (3.3%)	0/16 (0%)
42	1/28 (3.6%)	1/15 (6.7%)
48	2/27 (7.4%)	1/18 (5.6%)
54	1/18 (5.6%)	1/10 (10%)
60	2/23 (8.7%)	0/14 (0%)

The numerator denotes the number of participants who had a non-severe suicidal rating at baseline (score < 4) and developed a severe suicidal rating (score ≥ 4) at a post-baseline visit based on MADRS Item 10. The denominator denotes the number of participants who had a non-severe suicidal rating at baseline and attended a post-baseline visit

patients with rapid cycling, utilizing frequent assessments of symptoms.

Previous analyses in a mixed, but predominantly unipolar TRD population, have suggested a reduction in rates of suicide and all-cause mortality associated with VNS treatment (Aaronson et al. 2017; Feldman et al. 2013). The significant reductions in suicidality seen in this post-hoc analysis of patients with TRBD treated with VNS Therapy suggests that such findings might be expected in a larger population of individuals with TRBD, though further research is required. Similarly, it is important to further explore whether the cost effectiveness of VNS Therapy, observed in mixed TRD populations (predominantly unipolar depression), will also be observed in TRBD patients (Feldman et al. 2013).

VNS Therapy is generally well tolerated as revealed in a meta-analysis of over 1000 patients with either unipolar or bipolar depression (Berry et al. 2013). Data regarding the impact of adverse effects of medication was not available in the specific sub-sample of bipolar patients reported here. However, in the complete sample of unipolar and bipolar patients in the registry study (Aaronson et al. 2017), medication adverse effects were assessed using the frequency, intensity, and burden of side effects rating (FIBSER) scale (Wisniewski et al. 2006). Based on this scale, the patients in the VNS + TAU group reported higher scores for frequency, severity, and burden of side effects at baseline, but at the 12 and 24 months timepoints, there were no significant differences between the groups (data available on request).

There was a significant difference in the proportion of bipolar I participants in the two groups (67% in TAU + VNS vs 47% in TAU) and it is possible that this, in part, impacted the results. A significant effect of VNS + TAU over TAU was seen for time-to-first response in bipolar I participants (HR = 2.1; 95% CI 1, 4.3). This was not evident in those with bipolar II disorder, though the event rate was such that it is not possible to draw meaningful conclusions regarding a bipolar I vs bipolar II difference in the effectiveness of VNS Therapy added to TAU. In addition, this registry study unfortunately did not collect formal ratings of manic symptoms, so it is not possible to infer the effects of VNS Therapy on elevated mood. A previous 12-month follow-up study of VNS Therapy that included 20 patients with bipolar disorder assessed manic symptoms (Rush et al. 2005). Two of the participants developed brief mild manic episodes that lasted 1 to 2 weeks, and there were two short periods of sub-syndromal hypomanic symptoms (about 1 to 3 days), during the first 3 months of treatment with VNS Therapy. One participant (with a baseline diagnosis of unipolar disorder) developed a manic episode during the subsequent 9 months of treatment with VNS Therapy. Additional data are required to address whether there are potential differential effects between bipolar I vs II and the effect of VNS Therapy on hypomanic/manic symptoms, and such data will hopefully become available following completion of the current ongoing RECOVER randomized trial in the USA and the RESTORE-LIFE registry in Europe.

The study had several additional limitations. Participants were not randomized to the treatment groups, and when VNS Therapy was an available treatment option, there appeared to be a tendency for the treatment to be utilized in patients with bipolar disorder who had a significant degree of pharmacological non-response (or intolerance) and who had a higher rate of ECT treatment history (54%). This rate of ECT usage is similar to that seen in the unipolar patients included in the registry (61%) who received VNS. In addition, there was no sham VNS for the “TAU” group. Therefore, it is not possible to conclude with high certainty that all the effects observed are exclusively related to treatment with adjunctive VNS Therapy. The higher baseline MADRS score in the VNS + TAU compared with TAU group might also mean that regression to the mean may have played a larger role in the VNS + TAU group. In this effectiveness trial, medications and all other treatments, such as TMS and ECT, could change during treatment for either treatment group. Furthermore, study participants and clinicians were knowledgeable about the care being given. However, the off-site central raters collecting the MADRS data were blind to both treatment group and the overall

clinical status of the study participants. The population examined limits generalizability, though it is of course reasonably representative of participants suffering from a significant degree of difficult to treat depression in the context of bipolar disorder. Suicidality was not assessed using a specific suicidality scale, but rather a single item in the MADRS. Finally, in this 5-year longitudinal study, the participant attrition over time limits our ability to address with significant sample sizes some of the questions that are posed.

Conclusions

VNS Therapy as an adjunctive treatment to TAU was more effective than TAU alone in reducing depressive symptomatology, and led to a greater reduction in suicidal ideation, and, on average, a more rapid antidepressant response. Further, the antidepressant effects observed in the VNS + TAU group vis-à-vis TAU were likely more durable. Together, these findings support previously observed findings that adjunctive VNS is an efficacious antidepressant treatment in very severe, treatment-resistant bipolar depression.

Abbreviations

CGI: Clinical Global Impression; ECT: Electroconvulsive therapy; ITT: Intent-to-treat; KM: Kaplan–Meier; MADRS: Montgomery–Åsberg Depression Rating Scale; QIDS-SR: Quick Inventory of Depressive Symptomatology–Self Report; TAU: Treatment-as-usual; TRBD: Treatment-resistant bipolar depression; TRD: Treatment-resistant depression; VNS Therapy: Vagus Nerve Stimulation Therapy.

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Authors' contributions

RHM-W, MTB, STA, CRC, and AJR participated in the design of the study. SS analyzed the past treatments received by the study participants. AK and TG performed the statistical analysis. AJR and RHM-W drafted the manuscript. All authors contributed to the data interpretation and contributed to the revisions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets and results related to the VNS TRD registry that are open access can be found at <https://clinicaltrials.gov/ct2/show/NCT00320372>. De-identified participant's data for the VNS TRD Registry will not be shared. Please contact the corresponding author for data requests.

Ethics approval and consent to participate

Study procedures were reviewed and approved by an institutional review board for each participating site. All enrolled participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

Dr. McAllister-Williams has received speaker honorarium fees, fees for consultancy, and/or support for research from AstraZeneca, Bristol Myers-Squibb, Compass Inc., Cyberonics, Eli Lilly, Ferrer, GlaxoSmithKline, Janssen, Janssen-Cilag, LivaNova PLC, Lundbeck, MagStim, Merck Sharp & Dohme, myTomorrows, Otsuka, Pfizer, Pulse, Roche, Servier, SPIMACO, Sunovion, Syntropharma, Wyeth, American Center for Psychiatry & Neurology in the United Arab Emirates, British Association for Psychopharmacology, European College of Neuropsychopharmacology, International Society for Affective Disorders, OCM Comunicaziona s.n.c., Qatar International Mental Health Conference, UK Medical Research Council, and Wiley; grant support from National Institute for Health Research Efficacy and Mechanism Evaluation Panel and Health Technology Assessment Panel; and non-financial support from COMPASS Pathways. Dr. Sousa has no competing interests to disclose. Dr. Kumar is a former employee of LivaNova USA PLC. Dr. Greco is an employee of LivaNova USA PLC. Dr. Bunker is a former employee and a current consultant of LivaNova USA PLC. Dr. Aaronson has received consulting fees from Genomind, LivaNova PLC, Alkermes, and Neuronetics; research support from Neuronetics; and speaker honorarium fees from Neurocrine, Otsuka, and Sunovion. Dr. Conway has received research support from Bristol-Myers Squibb, the Stanley Medical Research Institute, the National Institute of Mental Health, NeoSync, Cyberonics, Taylor Family Institute for Innovative Psychiatric Research, The American Foundation for Suicide Prevention, Assurex Health Inc., August Busch IV Foundation, and Barnes-Jewish Hospital Foundation; and he is currently serving as a research consultant to LivaNova PLC. Dr. Rush has received consulting fees from Akili Interactive Labs, Inc., Brain Resource, Compass Inc., Curbstone Consultant LLC, Emmes Corp., Holmusk, Inc., LivaNova PLC, Johnson and Johnson (Janssen), and MindLinc; speaking fees from LivaNova PLC; and royalties from Guilford Press and the University of Texas Southwestern Medical Center Dallas, TX (for the Inventory of Depressive Symptoms and its derivatives); and he is also named co-inventor on 2 patents: US Patent No. 7,795,033: Methods to Predict the Outcome of Treatment with Antidepressant Medication (Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S, Wilson AS) and US Patent No. 7,906,283: Methods to Identify Patients at Risk of Developing Adverse Events During Treatment with Antidepressant Medication (Inventors: McMahon FJ, Laje G, Manji H, Rush AJ, Paddock S).

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Vagal nerve stimulation for epilepsy and depression HTCC final approval of coverage decision

(From page 7 of decision aid)

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 unclear outcome (i.e., tie), chair will lead discussion to determine next steps.

**Health Technology Clinical Committee
DRAFT Findings and Decision**

Topic: Stem cell therapy for musculoskeletal conditions
Meeting Date: June 12, 2020
Final Adoption: Pending

Meeting materials and transcript are available on the [HTA website](#).

Number and coverage topic:

20200612A – Stem cell therapy for musculoskeletal conditions

HTCC coverage determination:

Stem cell therapy for musculoskeletal conditions is **not a covered benefit**.

HTCC reimbursement determination:

Limitations of coverage:

N/A

Non-covered indicators:

Agency contact information:

Agency	Phone Number
Labor and Industries	1-800-547-8367
Public Employees Health Plan	1-800-200-1004
Washington State Medicaid	1-800-562-3022

Draft

HTCC coverage vote and formal action:

Committee decision

Based on the deliberations of key health outcomes the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and state agency utilization information. The committee decided that the current evidence on stem cell therapy for musculoskeletal conditions is sufficient to make a determination on this topic. The committee discussed and voted on the evidence for the use of stem cell therapy for musculoskeletal conditions. The committee considered the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

Based on these findings, the committee voted to not cover stem cell therapy for musculoskeletal conditions.

	Not covered	Covered under certain conditions	Covered unconditionally
Stem cell therapy for musculoskeletal conditions	10	0	0

Discussion

The committee reviewed and discussed the available studies for use of stem cell therapy for musculoskeletal conditions. Details of study design, inclusion criteria, outcomes and other factors affecting study quality were discussed. A clinical expert member provided detailed insight and discussion points. All committee members found the evidence sufficient to determine that use of stem cell therapy for musculoskeletal conditions is unproven for efficacy. A majority of committee members found the evidence sufficient to determine the use of stem cell therapy for musculoskeletal conditions is unproven for cost-effectiveness. Based on the evidence presented, all members of the committee found the use of stem cell therapy for musculoskeletal conditions to be either less safe than comparators, or unproven.

Limitations

N/A

Action

The committee checked for availability of a Centers for Medicare and Medicaid Services (CMS) national coverage decision (NCD). There is no Medicare national or local coverage determination for stem cell therapy for musculoskeletal conditions.

Five evidence based clinical guidelines and consensus statements were identified for this review. The committee discussed guidelines from the following organizations related to the use of stem cells for the treatment of musculoskeletal conditions:

- American Society of Interventional Pain Physicians (ASIPP), Responsible, Safe, and Effective Use of Biologics in the Management of Low Back Pain: ASIPP Guidelines, 2019
- International Society for Stem Cell Research (ISSCR), Current State of Cell-based Therapies for Osteoarthritis, 2019

- Australasian College of Sports Physicians (ACSP), ACSP—Position Statement: The Place of Mesenchymal Stem/Stromal Cell Therapies in Sport and Exercise Medicine, 2016
- International Society for Stem Cell Research (ISSCR), Guidelines for Stem Cell Research and Clinical Translation, 2016
- American Academy of Orthopaedic Surgeons (AAOS), Optimizing Clinical Use of Biologics in Orthopaedic Surgery: Consensus Recommendations From the 2018 AAOS/NIH U-13 Conference, 2018

The committee's coverage determination is consistent with the identified guidelines.

The committee discussion included concerns published by the Food and Drug Administration (FDA), and detailed in the evidence report.

The committee chair directed HTA staff to prepare a findings and decision document on the use of stem cell therapy for musculoskeletal conditions for public comment to be followed by consideration for final approval at the next public meeting.

Health Technology Clinical Committee Authority:

Washington State's legislature believes it is important to use a science-based, clinician-centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority (HCA), through its Health Technology Assessment (HTA) program, to engage in an evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company and that takes public input at all stages.

Pursuant to RCW 70.14.110 a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State HTCC determines how selected health technologies are covered by several state agencies (RCW 70.14.080-140). These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases its decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Director.

Stem cell therapy for musculoskeletal conditions

Draft findings and decision
Timeline, overview and comments

The Health Technology Assessment (HTA) program received comments in response to the posted Health Technology Clinical Committee (HTCC) draft findings and decision on stem cell therapy for musculoskeletal conditions.

Timeline

Phase	Date	Public Comment Days
Technology recommendations published	March 13, 2019	
Public comments	March 13 to 27, 2019	15
Selected technologies published	April 1, 2019	
Public comments	April 1 to 30, 2019	30
Draft key questions published	September 19, 2019	
Public comments	September 19, to October 2, 2019	14
Final key questions published	October 18, 2019	
Draft report published	December 31, 2019	
Public comments	December 31 to January 29, 2020	30
Final report published	February 19, 2020	
Public meeting	June 12, 2020*	
Draft findings & decision published	June 16, 2020	
Public comments	June 16 to 29, 2020	14
	Total	103

* Originally scheduled for March 20, 2020.

Overview

Category	Comment Period June 16 to 29, 2020	Cited Evidence
Patient, relative, and citizen	0	0
Legislator and public official	0	0
Health care professional	0	0
Industry and manufacturer	0	0
Professional society & advocacy organization	0	0
Total	0	0

Comments

Respondents	Cited Evidence
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1.

No public comment was received on the draft findings and decision.

Stem cell therapy for musculoskeletal conditions

HTCC final approval of coverage decision

(From page 7 of decision aide)

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.

- Based on public comment was evidence overlooked in the process that should be considered?
- 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 unclear outcome (i.e., tie), chair will lead discussion to determine next steps.