Washington State Health Care Authority

Vagal Nerve Stimulation for Epilepsy and Depression

Final Evidence Report

April 14, 2020

Health Technology Assessment Program (HTA)

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This health technology assessment report is based on research conducted by the Center for Evidence-based Policy (Center) under contract to the Washington State Health Care Authority (HCA). This report is an independent assessment of the technology question(s) described based on accepted methodological principles. The findings and conclusions contained herein are those of the authors, who are responsible for the content. These findings and conclusions do not necessarily represent the views of the Washington HCA and thus, no statement in this report shall be construed as an official position or policy of the HCA.

The information in this assessment is intended to assist health care decision makers, clinicians, patients, and policy makers in making evidence-based decisions that may improve the quality and cost-effectiveness of health care services. Information in this report is not a substitute for sound clinical judgment. Those making decisions regarding the provision of health care services should consider this report in a manner similar to any other medical reference, integrating the information with all other pertinent information to make decisions within the context of individual patient circumstances and resource availability.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

µsec	microsecond
ABVN	auricular branch of the vagus nerve
AED	antiepileptic drug
AEP	Adverse Event Profile
AHRQ	Agency for Healthcare Research and Quality
ASD	autism spectrum disorder
BDI	Beck Depression Inventory
BMP	best medical practice
CBT	cognitive behavioral therapy
CC	corpus callosotomy
CDRS	Cornell Dysthymia Rating Scale
CED	Coverage with Evidence Development
CES-D	Centre for Epidemiologic Studies Depression
CGI-I	Clinical Global Impression – Improvement scale
CGI-S	Clinical Global Impression – Severity scale
CI	confidence interval
CMS	Centers for Medicare & Medicaid Services
CNS	central nervous system
CPS	complex partial seizure
DBS	deep brain stimulation
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision
ECT	electroconvulsive therapy
ED	emergency department
EEG	electroencephalogram
FDA	U.S. Food and Drug Administration

GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
GTC	generalized tonic-clonic
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Depression Rating Scale (see also HRSD)
HRSD	Hamilton Rating Scale for Depression (see also HAM-D)
HR	hazard ratio
Hz	Hertz
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICER	incremental cost-effectiveness ratio
IDS-C	Inventory of Depressive Symptomatology – Clinician version
IDS-SR	Inventory of Depressive Symptomatology – Self-Report version
ILAE	International League Against Epilepsy
IQR	interquartile range
ITT	intent-to-treat
KQ	key question
LOCF	last observation carried forward
LS	least-square
LSSS	Liverpool Seizure Severity Scale
mA	milliamp
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MAUDE	Manufacturer and User Facility Device Experience
MD	mean difference
MDD	major depressive disorder
MDE	major depressive episode
MID	minimal important difference
MINI	Mini International Neuropsychiatric Interview

MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
MSAC	Australian Government Medical Services Advisory Committee
mTOR	mammalian target of rapamycin
NA	not applicable
NCD	National Coverage Decision
NDDI-E	Neurological Disorders Depression Inventory-Epilepsy
NHS3	Chalfont Seizure Severity Scale
NICE	National Institute for Health and Care Excellence
NR	not reported
NRS	nonrandomized study
OC	observed case
OR	odds ratio
PY	person-year
QALY	quality-adjusted life year
QIDS-C	Quick Inventory of Depressive Symptomatology – Clinician version
QIDS-SR	Quick Inventory of Depressive Symptomatology – Self Report version
QoL	quality of life
QOLIE-31-P	Quality of Life in Epilepsy Inventory–31-P
QOLIE-89	Quality of Life in Epilepsy Inventory-89
SD	standard deviation
RCT	randomized controlled trial
RNS	responsive neurostimulation
RR	risk ratio
SD	standard deviation
SE	standard error
SF	Short-Form health survey

SGS	secondary generalized seizure
SIGN	Scottish Intercollegiate Guidelines Network
SMR	standardized mortality rate
SPS	simple partial seizure
SSRI	selective serotonin reuptake inhibitor
SUDEP	sudden unexpected death in epilepsy
TAU	treatment as usual
TCA	tricyclic antidepressant
TRD	treatment-resistant depression
tVNS	transcutaneous VNS
UN	United Nations
VNS	vagal nerve stimulation

Executive Summary

Structured Abstract

Purpose

This report reviews the effectiveness and cost-effectiveness of vagal nerve stimulation (VNS) for epilepsy and depression.

Data Sources

We searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Ovid MEDLINE Epub Ahead of Print from 1946 to October 10, 2019; the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials from database inception to October 10, 2019; PsycINFO from 1806 to October 10. 2019; the National Library of Medicine clinical trials registry to December 2019; relevant professional society and organization clinical practice guidelines; and public and private payer coverage policies.

Study and Guideline Selection

Using *a priori* criteria, we conducted dual independent title and abstract screening and full-text article review for English language randomized controlled trials (RCTs), observational studies, and economic evaluations of VNS for epilepsy and depression. A third reviewer settled discrepancies. We also selected relevant clinical practice guidelines, using a similar process.

Data Extraction and Risk of Bias Assessment

One researcher used standardized procedures to extract data from the included studies and a second researcher checked all data entry for accuracy. We performed dual independent risk-of-bias assessment on the included studies and guidelines. A third reviewer settled discrepancies.

Data Synthesis and Analysis

We applied the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group system to rate the overall quality of evidence on selected measures of outcomes for epilepsy and depression.

Results

Epilepsy

High-stimulation VNS is associated with reduced seizure frequency when compared with low-stimulation VNS (very low- to low-quality evidence). VNS is also associated with similar reductions in seizure frequency compared to ongoing medication or surgery (very-low-quality evidence). People with a VNS implant may experience changes in their voice or hoarseness and some breathlessness, but in general, the rates of adverse effects are no different than low-stimulation VNS or treatment-as-usual (TAU; very-low- to moderate-quality evidence). Adverse events, such as hoarseness and coughing, are often transient and tend to decrease over time. In some cases, adverse events can be minimized through adjustment of the stimulation parameters.

Evidence about the cost-effectiveness of VNS is limited, with VNS being more costly and less effective than other strategies for children with drug-resistant tuberous sclerosis complex over a 5 year period. However, VNS may be cost-saving over 5 years in children aged 12 and older with

drug-resistant epilepsy with partial-onset seizures. There is a lack of cost-effectiveness evidence for longer durations of treatment.

We identified 1 RCT which did not demonstrate any benefit of transcutaneous VNS (tVNS) for epilepsy, and the guidelines and coverage policies which mentioned tVNS were not supportive of its use for seizure disorders. We did not identify any eligible studies reporting the economic outcomes of tVNS for epilepsy.

Depression

High-stimulation VNS is associated with an increased response rate (as measured on the Montgomery-Åsberg Depression Rating Scale [MADRS]) when compared with low-stimulation VNS (low-quality evidence), but other outcomes, such as reduced depression severity using other scales, and suicide or suicide attempts, are not different between stimulation groups (very low-low-quality evidence). VNS with TAU reduced depressive symptoms more than TAU alone (very-low-quality evidence); however, the difference was small and may not be clinically meaningful. VNS with TAU also resulted in higher rates of response compared with TAU alone (very-low-quality evidence). Other outcomes were not significantly different between groups (sham VNS or TAU) or were inconsistent, making it difficult to draw robust conclusions about the effectiveness of VNS for depression in adults. As with the use of VNS for epilepsy, patients using the VNS implant may experience voice alteration or hoarseness and coughing related to the use of VNS (very-low- to moderate-quality evidence).

We identified 1 RCT that did not demonstrate any consistent evidence of a benefit of tVNS for depression.

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

Clinical Practice Guidelines and Payer Policies

Overall, there is a high level of agreement across the clinical practice guidelines and coverage determinations.

Both of the good-methodological-quality guidelines, from the U.K.'s National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN), recommend VNS as adjunctive therapy for adults with drug-resistant epilepsy who are not suitable candidates for surgery. NICE recommends VNS an adjunctive therapy for children and young people whose epilepsy is refractory to antiepileptic medication, but who are not eligible for resective surgery. NICE also recommends VNS as an option for adults and children whose epileptic disorder is dominated by focal seizures (with or without secondary generalization) or generalized seizures. In guidelines that cover treatment of depression, VNS tends to be discouraged or only used in specific circumstances (i.e., in research only, or only after trying a range of other evidence-based depression treatments, including selective serotonin reuptake inhibitors [SSRIs]).

Medicare and the 3 commercial payers we reviewed cover VNS for the management of seizures, as well as covering revision or replacement of the implant or battery. None of the reviewed policies specified any age restrictions. Medicare will cover the use of VNS for treatment-resistant

depression (TRD) if the patient is registered in a study approved by the Centers for Medicare & Medicaid Services (CMS). The other payers we reviewed do not cover VNS for depression. All of the commercial payers we reviewed consider the use of tVNS experimental and investigational.

Conclusions

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

Background

Vagal, or vagus, nerve stimulation (VNS) is a treatment option for a limited number of individuals with severe epilepsy whose disease is not adequately controlled with other treatments. In 1997, the U.S. Food and Drug Administration (FDA) approved the use of VNS as an adjunctive therapy for reducing the frequency of seizures in adults and adolescents older than 12 years of age with partial onset seizures refractory to antiepileptic drugs (AEDs).[1] Following FDA approval, in 1999 the CMS issued a national coverage decision (NCD) to cover VNS for patients with medically refractory partial onset seizures, for whom surgery is not recommended or for whom surgery has failed.[2] In 2017, the FDA lowered the age of use in children from 12 years of age to 4 years of age.[1] Transcutaneous VNS (tVNS) is not currently FDA-approved for use in epilepsy. Because of the expanded indication for the use of VNS, there is interest in the clinical and cost-effectiveness evidence for the use of VNS and tVNS for epilepsy.

TRD is commonly defined as a failure of treatment to produce response or remission for patients after 2 or more treatment attempts of adequate dose and duration, but no clear consensus exists about this definition.[3] VNS is approved by the FDA for the adjunctive long-term treatment of chronic or recurrent depression for adults who are experiencing a major depressive episode and have not had an adequate response to adequate trials of 4 or more antidepressant treatments.[4] tVNS is not currently FDA approved for use in depression.

In 2006, CMS received a request to expand the NCD on VNS for epilepsy to include coverage of VNS for TRD in patients who had either been previously treated with or refused electroconvulsive therapy (ECT) for the treatment of depression, or who had been previously hospitalized for depression.[2] The specific indication requested for VNS coverage was for the adjunctive long-term treatment of chronic or recurrent depression in adults who were experiencing a major depressive episode and had not had an adequate response to 4 or more adequate depression treatments.[2] In 2007, CMS concluded there was sufficient evidence that VNS was not reasonable and necessary for TRD and it has remained noncovered.[2] In 2019, CMS issued a decision memo on the use of VNS for depression in the context of research only.[2] Therefore, questions remain on the clinical and cost-effectiveness of VNS and tVNS for TRD.

Technology of Interest

VNS is a neuromodulatory therapy that sends electric signals to specific brain structures via known pathways and systems.[5-7] A small device, called a pulse generator, is implanted into the left side of the chest to produce repeating, low-level pulses of electrical current that are transmitted via electrical leads along the vagus nerve and ultimately to the brainstem.[5] The left vagus nerve is chosen to minimize specific side effects.[8] tVNS targets the cutaneous receptive field of the auricular branch of the vagus nerve (ABVN) at the outer ear, and can be a noninvasive alternative to the implanted or invasive VNS for some conditions.[9] The mechanism of action of VNS is not fully understood, but is assumed to involve the neuromodulatory action of the vagus nerve, resulting in antiseizure effects and changes in mood, behavior, and cognition.[10]

Policy Context

VNS can be a treatment option for adults and children with epilepsy, and adults with TRD. Uncertainty exists regarding the appropriateness of VNS and tVNS for different types of epilepsy

and the use of VNS and tVNS for depression. The Washington Health Technology Assessment program selected this topic for assessment because of high concerns for the safety of VNS and tVNS and medium concerns around efficacy and costs.

This evidence review will help inform Washington's independent Health Technology Clinical Committee as the committee determines coverage regarding VNS for epilepsy and depression.

Methods

This evidence review is based on the final key questions (KQs) published on November 13, 2019.[11] The draft KQs were available for public comment from October 16 to October 29, 2019, and appropriate revisions were made to the KQs based on the comments and responses.[12] All public comments received and a table of responses can be found on the Washington Health Technology Assessment website. The draft report was available for public comment between February 27 and March 30, 2020, and appropriate revisions based on comments were made and posted to the program's website. The draft report was peer-reviewed by independent subject matter experts, and appropriate revisions are reflected in this final report.

Key Questions

Epilepsy

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

Depression

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

[1] VNS includes both the invasive and transcutaneous versions in the key questions, but in the remainder of the text VNS refers to the invasive version and tVNS to transcutaneous VNS.

Data Sources and Searches

We searched Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, and Ovid MEDLINE Epub Ahead of Print from 1946 to October 10, 2019; the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials from database inception to October 10, 2019; PsycINFO from 1806 to October 10. 2019; the National Library of Medicine clinical trials registry to December 2019; relevant professional society and organization clinical practice guidelines; and public and private payer coverage policies.

Study and Guideline Selection

Using *a priori* criteria, we conducted dual independent title and abstract screening and full-text article review for English language randomized controlled trials (RCTs), observational studies, and economic evaluations of VNS in epilepsy and depression. A third reviewer settled discrepancies. We also selected relevant clinical practice guidelines, using a similar process.

Data Abstraction and Quality Assessment

One researcher used standardized procedures to extract data from the included studies and a second researcher checked all data entry for accuracy. We performed dual independent risk-of-bias assessment on the included studies and guidelines. A third reviewer settled discrepancies.

Data Analysis and Synthesis

We combined data in meta-analyses for the key outcomes of response (i.e., a 50% reduction in seizures and depression severity response, as defined by each specific measure) and adverse events using Review Manager.[13] For the epilepsy outcomes, we used data from the published Cochrane review[10] and planned to update the results with additional eligible trials, as appropriate. We assigned selected outcomes a summary judgment for the overall quality of evidence (Appendix E) using GRADE.[14,15] We selected the outcomes of seizure frequency, seizure freedom, seizure severity, depression severity, suicide, response rates, withdrawals, and common adverse events (e.g., voice alteration, cough, pain) from measures of effectiveness and safety.

Results

Our searches returned a total of 1,168 records published since 2009 (the search date in the prior report[16]). We also checked the reference lists of relevant systematic reviews[10,17-48] and added a further 7 studies for review.[49-55] In total, 9 RCTs (in 13 publications) and 20 nonrandomized studies (NRSs; in 23 publications) met our inclusion criteria for KQs 1, 2, and 3.[49-51,55-87] Two economics studies also met the inclusion criteria for KQ 4.[88,89]

Key Questions 1 and 2

Epilepsy

We found 20 studies, reported in 23 publications, which evaluated the benefits and harms of VNS for epilepsy.[49-51,55,58,60,63,64,66-69,71-73,75-77,80,82,83,86,87] We also found 1 RCT that evaluated the benefits and harms of tVNS for epilepsy.[79]

High- vs. Low-Stimulation VNS

- High-stimulation VNS was associated with more individuals having a 50% or more reduction in seizure frequency (low-quality evidence, based on 3 RCTs) and a reduced mean seizure

frequency (very-low-quality evidence, based on 1 RCT) than low-stimulation VNS, but similar rates of seizure freedom (low-quality evidence, based on 2 RCTs).
- High-stimulation VNS was associated with higher levels of voice alteration or hoarseness than low-stimulation VNS (moderate-quality evidence, based on 2 RCTs), and higher levels of dyspnea than low-stimulation VNS (low-quality evidence, based on 2 RCTs), but similar rates of withdrawals, cough, pain, paresthesias, nausea, and headache (very-low-quality of evidence, based on 1 to 3 RCTs, depending on the outcome).

VNS vs. Treatment as Usual

- VNS was more effective in reducing seizure frequency than TAU or ongoing medication (very-low-quality evidence, based on 4 NRSs) but similar in rates of response, defined as a 50% or more reduction in seizures (low-quality evidence, based on 1 RCT) and seizure freedom (very-low-quality evidence, based on 4 NRSs).
- VNS was associated with similar number of withdrawals, voice alteration or hoarseness, pain, paresthesias, and headache as TAU (very-low- to low-quality evidence, based on 1 RCT).

VNS vs. Surgery

- VNS and surgery were similarly effective in reducing seizure frequency, but this was not consistent across studies (very-low-quality evidence, based on 4 NRSs). VNS was less effective than surgery for increasing rates of seizure freedom; again, this was not consistent across studies (very-low-quality evidence, based on 5 NRSs).

VNS vs. Responsive Neurostimulation

- VNS and responsive neurostimulation appear similarly effective in reducing seizure frequency, but this was not consistent across studies (very-low-quality evidence, based on 2 NRSs). They also appear similarly effective in terms of seizure freedom, but results are not consistent (very-low-quality evidence, based on 2 NRSs).

High- vs. Low-Stimulation tVNS

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

Longer-term Safety Outcomes

- Based on 1 registry study, laryngeal symptoms (including hoarseness and coughing) and local dysesthesias related to VNS use tended to decrease over time while rates of high-lead impedance tended to increase. Other adverse events, such as cardiac or respiratory complications and local infections, were low at all time points.

Depression

We found 5 studies, reported in 9 publications, which evaluated the benefits and harms of VNS for depression.[56,59,61,62,70,74,78,84,85] We also found 1 RCT that evaluated the benefits and harms of tVNS for depression.[81]

High- vs. Low-Stimulation VNS

- High-stimulation VNS had higher rates of response, defined as 50% MADRS reduction, compared with low-stimulation VNS (low-quality evidence, based on 1 RCT), but was not associated with reduced depression severity (low-quality evidence, based on 1 RCT) or lower rates of suicide or attempted suicide (very-low-quality evidence, based on 1 RCT).
- High-stimulation and low-stimulation VNS had similar number of withdrawals, rates of voice alteration or hoarseness, cough, dyspnea, pain, nausea, and headache (very-low- to low-quality evidence, based on 1 RCT).

VNS vs. Sham VNS

- Compared with sham VNS, VNS was not associated with reduced depression severity (moderate-quality evidence, based on 1 RCT), or with lower rates of suicides (very-low-quality evidence, based on 1 RCT). VNS and sham VNS also had similar rates of response, defined as 50% MADRS reduction (very-low-quality evidence, based on 1 RCT).
- VNS, when compared with sham VNS, has higher levels of voice alteration or hoarseness and cough (moderate-quality evidence, based on 1 RCT), but similar number of withdrawals, dyspnea, pain, paresthesias, and nausea (very-low- to low-quality evidence, based on 1 RCT).

VNS vs. Treatment as Usual

- VNS with TAU was more effective in reducing depression symptoms and had higher response rates than TAU alone (very-low-quality evidence, based on 1 NRS), but may be associated with higher rates of attempted suicide or self-inflicted injury, but the evidence is very uncertain and may reflect greater severity of depression (very-low-quality evidence, based on 1 NRS). VNS may be associated with lower mortality rates, but study results are not consistent (very-low-quality evidence, based on 2 NRS).
- VNS has lower withdrawal rates than TAU (very-low-quality evidence, based on 1 NRS).

tVNS vs. Sham tVNS

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

FDA-reported Harms for Epilepsy and Depression

The types of adverse events reported to the FDA appear similar to those reported in our eligible studies for epilepsy and depression.

Recalls documented in the Medical Device Recall database included errors in impedance measurements, unintended warning messages, miscalculations resulting in inappropriate VNS

stimulation (higher and lower levels of stimulation than expected), reductions in device and battery longevity, and lead fractures.

In December 2019, the FDA issued a Class I recall, the most serious type of recall, where problems with the recalled devices may cause serious injuries or death.[90] The FDA reported that LivaNova is recalling the VNS Therapy SenTiva Generator System due to an unintended reset error that causes the system to stop delivering VNS therapy.[90] If device replacement is needed, there is a risk associated with additional surgery to replace the generator.[90] The FDA issued guidance to patients and health care providers on actions they should take to ensure the risk of serious injury or death is minimized.[90]

Key Question 3

Epilepsy

We identified a further 2 NRSs evaluating the benefits and harms of VNS by patient characteristic.[57,65]

Prior Cranial Surgery

Patients who had VNS after prior cranial surgery had lower rates of response, defined as a 50% reduction or more in seizure frequency at 12 months, but not at 24 months.[57] Both groups reported similar levels of seizure freedom at 12 and 24 months.[57]

Early or Late Treatment with VNS

We identified 1 study comparing early treatment with VNS (6 years or less after the onset of seizures) and late treatment with VNS (more than 6 years after the onset of seizures).[65] Patients in the early and late treatment groups had similar reductions in seizure frequency and response rates.[65] However, patients treated in the early treatment group were more likely to become seizure-free at 12 months.[65]

Depression

Prior ECT

Patients in the VNS+TAU group who had previously responded to ECT had higher response rates than patients in the TAU group. Patients in the VNS+TAU group who had not previously responded to ECT also had higher response rates than patients in the TAU group.

Comorbid Anxiety

Individuals with comorbid anxiety had similar rates of response to VNS to those without comorbid anxiety disorders.[56]

Type of Depression (unipolar vs. bipolar)

The effectiveness of VNS did not appear to differ by type of depression (unipolar vs. bipolar).[56,62,84]

Age

Mortality rates were significantly lower in the VNS group than the TRD and managed depression groups overall, but not for the subgroup of people under 40 years of age.[61]

Key Question 4

Epilepsy

- VNS was more costly and less effective than other strategies for children with drug-resistant tuberous sclerosis complex who have not responded to 2 or 3 AEDs (very-low-quality evidence, based on 1 cost-utility study in this specific population).
- VNS was associated with a reduction in costs over 5 years compared with AEDs alone (very-low-quality evidence, based on 1 budget impact study).

We did not identify any studies reporting on economic outcomes related to the use of tVNS for epilepsy.

Depression

We did not identify any studies reporting on economic outcomes related to the use of VNS or tVNS for depression.

Summary

Epilepsy

High-stimulation VNS is associated with reduced seizure frequency when compared with low-stimulation VNS (very-low to low-quality evidence). VNS is also associated with similar reductions in seizure frequency compared to ongoing medication or surgery (very-low-quality evidence). People with a VNS implant may experience changes in their voice or hoarseness and some breathlessness, but in general, the rates of adverse effects are no different to low-stimulation VNS or TAU (moderate- to very-low-quality evidence). Adverse events, such as hoarseness and coughing, were often transient and tended to decrease over time. In some cases, adverse events could be minimized through adjustment of the stimulation parameters. We identified 1 RCT which did not demonstrate any benefit of tVNS for epilepsy.

Depression

High-stimulation VNS is associated with an increased response rate (as measured on the MADRS) when compared with low-stimulation VNS (low-quality evidence), but other outcomes, such as reduced depression severity using other scales, and suicide deaths or attempts, are not different between stimulation groups (very-low to low-quality evidence). VNS with TAU reduced depressive symptoms more than TAU alone (very-low-quality evidence); however, the difference was small and may not be clinically meaningful. VNS with TAU also resulted in higher rates of response compared with TAU alone (very-low-quality evidence). Other outcomes were no different between groups (sham VNS or TAU) or were inconsistent, making it difficult to draw robust conclusions about the effectiveness of VNS for depression in adults. As with the use of VNS for epilepsy, patients using the VNS implant may experience voice alteration or hoarseness and coughing related to the use of VNS (very-low to moderate-quality evidence). We identified 1 RCT that did not demonstrate any consistent evidence of a benefit of tVNS for depression.

Clinical Practice Guidelines

Epilepsy

We identified 6 eligible guidelines on the use of VNS or tVNS for epilepsy.[91-96] The 2 good-methodological-quality guidelines from NICE[93] and SIGN[94] recommended VNS as adjunctive

therapy for adults with drug-resistant epilepsy who are not candidates for surgery. NICE also recommended VNS an adjunctive therapy for children and young people whose epilepsy is refractory to AEDs, but who are not candidates for resective surgery.[93] NICE stated that VNS is an option for adults and children whose epileptic disorder is dominated by focal seizures (with or without secondary generalization) or generalized seizures.[93] SIGN was expected to publish a guideline on the diagnosis and management of epilepsy in children in 2019, but at the time of writing this report, no publication was identified.[94]

The fair-methodological-quality guideline from the Task Force Report for the International League Against Epilepsy (ILAE) Commission of Pediatrics also recommended that infants with medically refractory seizures who are not suitable candidates for epilepsy surgery may be considered for VNS.[95] However, the Task Force did note there were insufficient data to conclude if there is a benefit from intervention with VNS in infants with seizures, and the recommendation was therefore based on expert opinion and standard practice, including receiving optimal level of care at specialist facilities.[95]

Only 1 guideline explicitly mentioned tVNS and it recommended against its use for drug-resistant epilepsy.[92]

Depression

We identified 5 eligible guidelines on the use of VNS or tVNS for depression.[97-101] The Working Group of the Clinical Practice Guideline on the Management of Depression in Adults,[101] assessed as good methodological quality, in 2014 recommended that the use of VNS for depression outside the scope of research was discouraged due to the invasive nature of the procedure, and uncertainty about its efficacy and adverse effects. A guideline by the Department of Veterans Affairs and Department of Defense,[98] assessed as fair methodological quality, made a similar recommendation against offering VNS for patients with MDD, including patients with severe TRD, outside of a research setting.[98] However, the other 2 fair-methodological-quality guidelines differed from these recommendations. In 2016, the Canadian Network for Mood and Anxiety Treatments[97] recommended VNS as a third-line treatment, after repetitive transcranial magnetic stimulation (first-line treatment) and ECT (second-line treatment) for adults with major depressive disorder. However, in 2015, the Royal Australian and New Zealand College of Psychiatrists[100] made no explicit recommendations on the use of VNS for depression. In 2018, the Australian Government Medical Services Advisory Committee[99] did not support public funding of VNS for chronic major depressive episodes, noting concerns about the comparative safety, the limited evidence of clinical effectiveness, and the resulting uncertainty on the comparative cost-effectiveness of VNS.

Selected Payer Coverage Determinations

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

The NCD currently states that[2]:

- VNS is reasonable and necessary for patients with medically refractory partial onset seizures for whom surgery is not recommended or for whom surgery has failed.

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

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

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

Ongoing Studies

We identified 3 ongoing studies (randomized and nonrandomized) that would be eligible for this evidence review.[103-105] One ongoing study is in epilepsy and 2 are in depression. The RECOVER trial, NCT03887715,[105] is currently the only CMS-approved RCT for VNS in depression.[2]

Conclusions

Epilepsy

High-stimulation VNS is associated with reduced seizure frequency when compared with low-stimulation VNS (very-low to low-quality evidence). VNS is also associated with similar reductions in seizure frequency to ongoing medication or surgery (very-low-quality evidence). People with a VNS implant may experience changes in their voice or hoarseness and some breathlessness, but in general, the rates of adverse effects are no different to low-stimulation VNS or TAU (moderate- to very-low-quality evidence). Adverse events, such as hoarseness and coughing, were often transient and tended to decrease over time. In some cases, adverse events could be minimized through adjustment of the stimulation parameters.

In 2017, the FDA considered new evidence for the expanded use of VNS for epilepsy in young children aged 4 and older.[1] The prior approval was limited to children aged 12 and older.[1] Based on an analysis of younger and older children and young adults in the pivotal trials used for the initial approval, a Japanese registry, and the Cyberonics Post-Market Surveillance database, the FDA concluded that[1]:

- VNS was an effective and safe treatment for the reduction of partial onset seizures in pediatric patients 4 to 11 years of age with refractory epilepsy.
- The 12-month responder rate for pediatric patients 4 to 11 years of age with partial onset seizures in the Japan post-approval study was 39% (95% credible interval, 28% to 52%).

- There were no unanticipated adverse device effects observed in pediatric patients 4 to 11 years of age. However, infection and extrusion of leads had a statistically greater incidence rate in patients 4 to 11 years of age compared to older children.
- Younger patients may have a greater risk for wound infection when compared to adolescents and adults; therefore, the importance of monitoring for site infection as well as the avoidance of manipulation of the surgical site post implant in children should be emphasized.
- Overall, treatment-emergent adverse events in patients 4 to 11 years of age were consistent with patients ≥ 12 years of age treated with VNS, and no new risks were identified.

In practice, people with drug-resistant epilepsy may have tried all the available and appropriate AEDs, and may also not be suitable candidates for surgery after a comprehensive assessment. In virtually all identified clinical practice guidelines, VNS is recommended as a treatment option for adults and children who are refractory to antiepileptic medication but are not suitable for resective surgery. The NCD for Medicare currently states that[2]:

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

Coverage polices from 3 commercial payers are also consistent in approving coverage for the management of medically-refractory seizures, as well as any necessary revision or replacement of the implant or battery. All of the commercial payers we reviewed consider the use of tVNS for epilepsy as experimental and investigational.

However, VNS may not be cost-effective in subgroups of people with specific types of seizure disorders (e.g., drug-resistant tuberous sclerosis complex) but the wider cost-effectiveness in patients 4 years of age and older with partial onset seizures that are refractory to AEDs remains unclear. One analysis estimated that VNS would result in reduced costs over 5 years compared with AEDs alone, but our confidence in this estimate was very low. There is a lack of cost-effectiveness evidence for longer durations of treatment.

We identified 1 RCT which did not demonstrate any benefit of tVNS for epilepsy, and the guidelines and coverage policies which mentioned tVNS were not supportive of its use for seizure disorders.

Depression

High-stimulation VNS is associated with an increased response rate (as measured on the MADRS) when compared with low-stimulation VNS (low-quality evidence), but other outcomes, such as reduced depression severity using other scales and suicide deaths or attempts, are not different between stimulation groups (very-low to low-quality evidence). VNS with TAU reduced depressive symptoms more than TAU alone (very-low-quality evidence); however, the difference was small and may not be clinically meaningful. VNS with TAU also resulted in higher rates of response compared with TAU alone (very-low-quality evidence). Other outcomes were not different between groups (sham VNS or TAU) or were inconsistent, making it difficult to draw robust conclusions about the effectiveness of VNS for depression in adults. As with the use of

VNS for epilepsy, patients using the VNS implant may experience voice alteration or hoarseness and coughing related to the use of VNS (very-low- to moderate -quality evidence).

Most guidelines either recommend against the use of VNS for depression, citing a lack of evidence and calling for more research, or did not make any specific recommendations for or against the use of tVNS for depression. However, 1 guideline did recommend VNS as a third-line treatment, after repetitive transcranial magnetic stimulation (first-line treatment) and ECT (second-line treatment) for adults with MDD.

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

There is a high level of agreement across the coverage determinations, with VNS for depression not being covered by any of the 3 commercial payers reviewed for this report.

We identified 1 RCT that did not demonstrate any evidence of a benefit of tVNS for depression, and the guidelines and coverage policies that mentioned tVNS were not supportive of its use for depression in adults.

We did not identify any studies reporting on economic outcomes related to the use of VNS or tVNS for depression.

FDA-reported Harms for Epilepsy and Depression

The types of adverse events reported to the FDA appear similar to those reported in our eligible studies for epilepsy and depression.

Recalls documented in the Medical Device Recall database included errors in impedance measurements, unintended warning messages, miscalculations resulting in inappropriate VNS stimulation (both higher and lower levels of stimulation than expected), reductions in device and battery longevity, and lead fractures (Appendix G).

In December 2019, the FDA issued a Class I recall, the most serious type of recall, where problems with the recalled devices may cause serious injuries or death.[90] The FDA reported that LivaNova is recalling the VNS Therapy SenTiva Generator System due to an unintended reset error that causes the system to stop delivering VNS therapy.[90] If device replacement is needed, there is a risk associated with additional surgery to replace the generator.[90] The FDA issued guidance to patients and health care providers on actions they should take to ensure the risk of serious injury or death is minimized.[90]

Clinical Practice Guidelines and Coverage Policies

Overall, there is a high level of agreement across the clinical practice guidelines and coverage determinations.

Both of the good-methodological-quality guidelines, from NICE and SIGN, recommend VNS as adjunctive therapy for adults with drug-resistant epilepsy who are not suitable candidates for surgery. NICE also recommended VNS an adjunctive therapy for children and young people whose epilepsy is refractory to antiepileptic medication, but who are not candidates for resective surgery. NICE also recommends VNS as an option for adults and children whose epileptic disorder is dominated by focal seizures (with or without secondary generalization) or generalized seizures. In guidelines for the treatment of depression, VNS tends to be discouraged, or only used in very specific circumstances (i.e., in research only, or only after trying a range of other evidence-based depression treatments).

Medicare and the 3 commercial payers we reviewed cover VNS for the management of seizures, as well as covering revision or replacement of the implant or battery. None of the reviewed policies specified any age restrictions. Three commercial payers we reviewed do not cover VNS for depression and consider the use of tVNS as experimental and investigational. Medicare covers the use of VNS for TRD if the patient is registered in a CMS-approved study.

Summary

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

Technical Report

Background

In 2015, an estimated 1.2% of the U.S. population had active epilepsy.[106] This is about 3.5 million people nationwide, representing 3 million adults and 470,000 children.[106] There are many different types of epilepsy, and most seizure types can be managed with lifestyle changes and medications. Vagal nerve stimulation (VNS) is a treatment option for a limited number of severely affected individuals whose disease is not adequately controlled with other treatments, including pharmacological management or surgery. Many people will respond to a first or second trial of an antiseizure medication, but if the second medication fails, the chance of response with additional medications is very low.[107] People whose disease is not adequately controlled with other treatments are also at an increased risk of sudden unexpected death in epilepsy (SUDEP).[108] In 1997, the U.S. Food and Drug Administration (FDA) approved the use of VNS as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents older than 12 years of age with partial onset seizures refractory to antiepileptic drugs (AEDs).[1] Following FDA approval, in 1999, the Centers for Medicare & Medicaid Services (CMS) issued a national coverage decision (NCD) to cover VNS for patients with medically refractory partial onset seizures, for whom surgery is not recommended or for whom surgery has failed.[2] In 2017, the FDA lowered the age of use in children from 12 years of age to 4 years of age.[1] Transcutaneous VNS (tVNS) is not currently FDA-approved for use in epilepsy. Because of the expanded indication for the use of VNS, there is interest in the clinical and cost-effectiveness evidence for the use of VNS and tVNS for epilepsy.

Major depression is one of the most common mental disorders in the United States.[109] In 2017, an estimated 17.3 million adults (7.1%) in the U.S. had at least 1 major depressive episode.[109] Many people with major depression respond to treatment with medication or psychological therapies, either alone or in combination.[110] However, up to 33% of people with major depressive disorder (MDD) will not respond to an adequate trial of antidepressant medication, and the chances of response tend to decline with each new trial of medication.[110] Treatment-resistant depression (TRD) is commonly defined as a failure of treatment to produce response or remission for patients after 2 or more treatment attempts of adequate dose and duration, but no clear consensus exists about this definition.[3] VNS is indicated for the adjunctive long-term treatment of chronic or recurrent depression for adults who are experiencing a major depressive episode and have not had an adequate response to 4 or more adequate antidepressant treatments.[4] tVNS is not currently FDA approved for use in depression.

In 2006, CMS received a request to expand the NCD on VNS for epilepsy to include coverage of VNS for TRD for patients who had either been previously treated with or refused electroconvulsive therapy (ECT) for the treatment of depression, or who had been previously hospitalized for depression.[2] The specific indication requested for VNS coverage was for the adjunctive long-term treatment of chronic or recurrent depression in adults who were experiencing a major depressive episode and had not had an adequate response to 4 or more adequate depression treatments.[2] In 2007, CMS concluded there was sufficient evidence that VNS was not reasonable and necessary for TRD and it has remained noncovered.[2] In 2019, CMS issued a decision memo on the use of VNS for depression in the context of research only[2]:

- CMS will cover FDA-approved VNS devices for TRD through Coverage with Evidence Development when offered in a CMS-approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least 1 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.

CMS's decision was based on a review of the literature, which concluded VNS for TRD seemed promising, but not convincing.[2] Coverage in the context of ongoing clinical research helps ensure the technology is provided to appropriate patients in controlled settings while developing evidence that the treatment improves health outcomes and is safe.[2] CMS also approved coverage for a VNS device replacement if it is required due to the end of battery life, or any other device-related malfunction in individuals currently implanted with a VNS device for TRD.[2] Questions therefore remain on the clinical and cost-effectiveness of VNS and tVNS for TRD.

Technology of Interest

Vagal, or vagus, nerve stimulation (VNS) is a neuromodulatory therapy that sends electric signals to specific brain structures via known pathways and systems.[5-7] A small device, called a pulse generator, is implanted into the left side of the chest to produce repeating, low-level pulses of electrical current that are transmitted via electrical leads along the vagus nerve and ultimately to the brainstem.[5] The left vagus nerve is chosen to minimize specific side effects.[8] Transcutaneous VNS (tVNS) targets the cutaneous receptive field of the auricular branch of the vagus nerve (ABVN) at the outer ear, and can be a noninvasive alternative to the implanted or invasive VNS for some conditions.[9] The mechanism of action of VNS is not fully understood, but is assumed to involve the neuromodulatory action of the vagus nerve, resulting in antiseizure effects and changes in mood, behavior, and cognition.[10]

Policy Context

VNS can be a treatment option for adults and children with epilepsy, and adults with TRD. Uncertainty exists regarding the appropriateness of VNS and tVNS for different types of epilepsy and the use of VNS and tVNS for depression. The Washington Health Technology Assessment program selected this topic for assessment because of high concerns for the safety of VNS and tVNS and medium concerns around efficacy and costs.

This evidence review will help inform Washington's independent Health Technology Clinical Committee as the committee determines coverage regarding VNS for epilepsy and depression.

Washington State Utilization and Cost Data

Populations

See Appendix K for this data.

Methods

See Appendix K for this data.

Findings

See Appendix K for this data.

Methods

This evidence review is based on the final key questions (KQs) published on November 13, 2019.[11] The draft KQs were available for public comment from October 16 to October 29, 2019, and appropriate revisions were made to the KQs based on the comments and responses.[12] All public comments received and a table of responses can be found on the Washington Health Technology Assessment website. The draft report was available for public comment between February 27 and March 30, 2020, and appropriate revisions based on comments were made and posted to the program's website. The draft report was peer-reviewed by subject matter experts, and appropriate revisions are reflected in this final report. The PICO statement (population, intervention, comparator, outcome), along with the setting, study design, and publication factors that guided development of the KQs and study selection are presented in Table 1 and Table 2 below.

Key Questions

Epilepsy

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

Depression

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

[2] VNS includes both the invasive and transcutaneous versions in the key questions, but in the remainder of the text VNS refers to the invasive version and tVNS to transcutaneous VNS.

Analytic Framework

Epilepsy

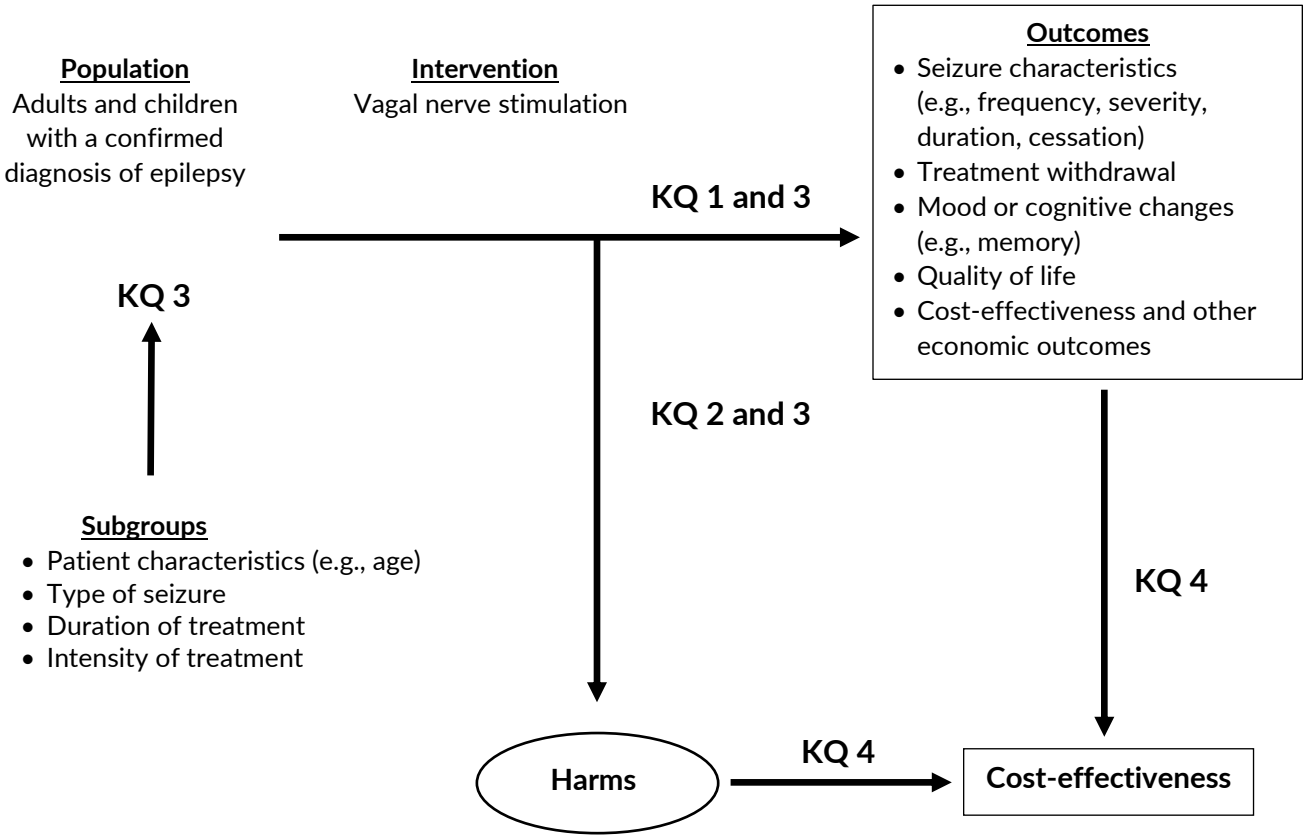

Figure 1. Analytic Framework: Epilepsy

Depression

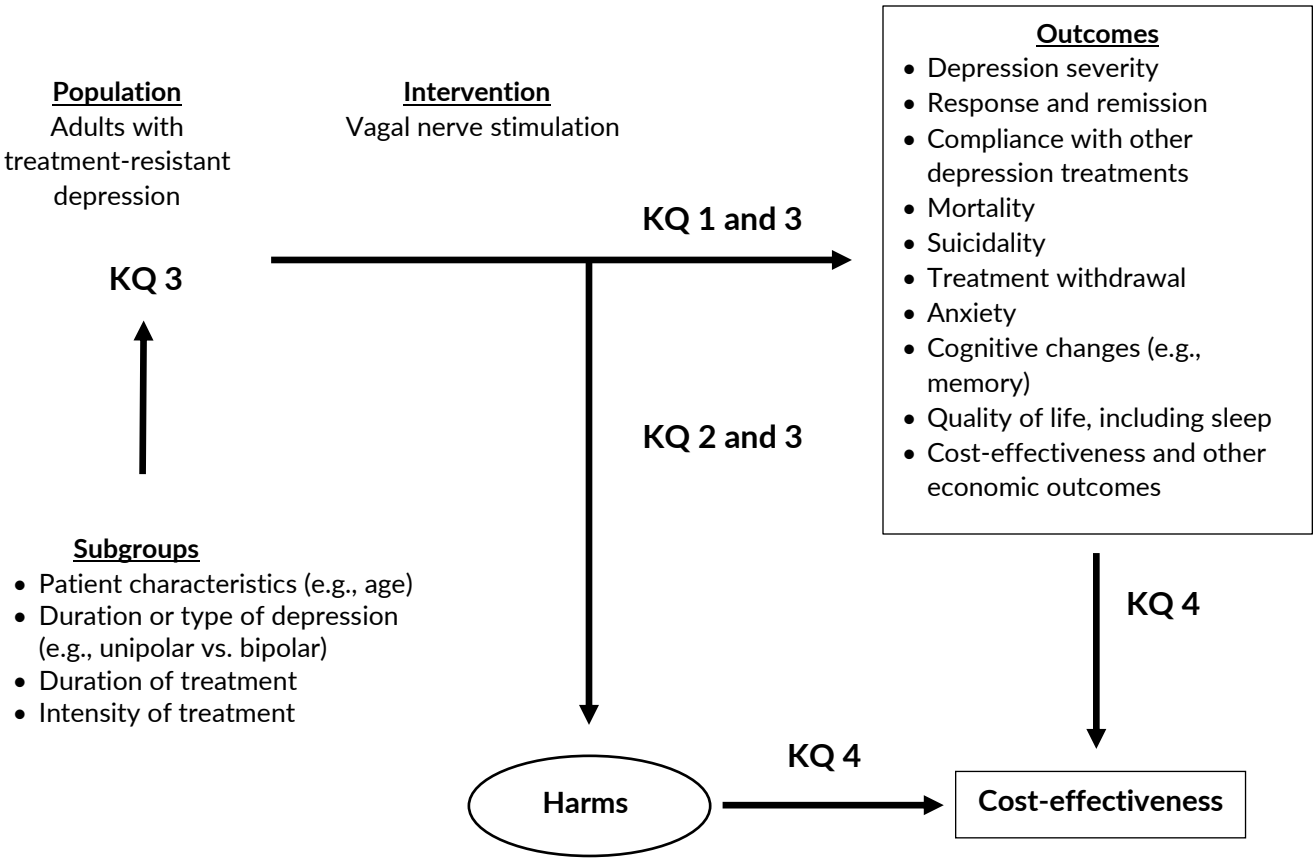

Figure 2. Analytic Framework: Depression

Eligible Studies

Table 1 and Table 2 summarize the study inclusion and exclusion criteria.

Table 1. Key Study Inclusion and Exclusion Criteria for Epilepsy

Study Component	Inclusion	Exclusion
Populations	• Adults and children (aged 4 and older) with epilepsy	• Studies including individuals with suspected epilepsy • Studies including individuals with seizures related to conditions other than epilepsy • Studies in individuals with pseudoseizures • Studies focused on the treatment of status epilepticus alone
Interventions	• VNS alone, or in combination with treatment as usual (e.g., antiepileptic medications) • tVNS alone, or in combination with treatment as usual (e.g., antiepileptic medications)	• Other CNS or vagal nerve stimulation techniques
Comparators	• Antiepileptic medication • Surgery • Other types of brain stimulation (invasive or noninvasive) • Sham VNS • VNS at a subtherapeutic level • No treatment	• Studies without a comparator intervention • Studies with indirect comparisons • Studies with an outdated comparator or a comparator intervention not available in the U.S.
Outcomes	• Primary outcomes: seizure frequency • Secondary outcomes: seizure cessation; seizure severity (measured with a validated tool); seizure duration; treatment withdrawal; mood or cognitive changes (e.g., depression, memory); quality of life (measured with a validated tool) • Safety: harms directly related to VNS (e.g., infection or hoarseness); reimplantation; failure rate • Economic: cost-effectiveness outcomes (e.g., cost per improved outcome) or cost-utility outcomes (e.g., cost per QALY, ICER)	• Other outcomes • Cost of VNS from studies performed in non-U.S. countries • Cost of VNS from studies performed in the U.S. that are older than 5 years
Setting	• Any outpatient or inpatient clinical setting in countries categorized as very high on the UN Human Development Index[111]	• Nonclinical settings (e.g., studies in healthy volunteers) • Countries categorized other than very high on the UN Human Development Index[111]

Study Component	Inclusion	Exclusion

Study Design	• Key Questions 1–4
	  ○ Randomized controlled trials
	  ○ Nonrandomized, comparative studies with 10 or more participants in each group
	• Additional studies/data for Key Questions 2 and 3 (harms)
	  ○ Governmental or other large, multisite registries with 100 or more participants and databases containing reports of procedure-related harms or device recalls (e.g., FDA MAUDE database, FDA Medical Device Recall database)
	• Additional studies/data for Key Question 4
	  ○ Cost-effectiveness studies and other formal comparative economic evaluations
		• Abstracts, conference proceedings, posters, editorials, letters
		• Nonrandomized, comparative studies with fewer than 10 participants in each group
		• Studies without a comparator
		• Proof-of-principle studies (e.g., technology development or technique modification)
		• Studies with harms outcomes for an intervention not included in Key Question 1
		• Registries with fewer than 100 participants

Publication	• Studies in peer-reviewed journals, technology assessments, or publicly available FDA or other U.S. government reports • Published in English • Published since June 2009 (search date in the original HTA report)	• Studies with abstracts that do not allow study characteristics to be determined • Studies that cannot be located • Duplicate publications of the same study that do not report different outcomes or follow-up times, or single site reports from published multicenter studies • Studies in languages other than English

Abbreviations. CNS: central nervous system; FDA: U.S. Food and Drug Administration; HTA: Washington health technology assessment; ICER: incremental cost-effectiveness ratio; MAUDE: Manufacturer and User Facility Device Experience; QALY: quality-adjusted life year; tVNS: transcutaneous VNS; UN: United Nations; VNS: vagal nerve stimulation.

Table 2. Key Study Inclusion and Exclusion Criteria for Depression

Study Component	Inclusion	Exclusion
Populations	• Adults (aged 18 and older) with TRD	• Studies including individuals with depression responsive to treatment • Studies including individuals with postpartum depression
Interventions	• VNS alone, or in combination with treatment as usual (antidepressant medications or nonpharmacological therapies) • tVNS alone, or in combination with treatment as usual (antidepressant medications or nonpharmacological therapies)	• Other CNS or vagal nerve stimulation techniques
Comparators	• Antidepressant medication • Nonpharmacological treatments (e.g., CBT) • Other types of invasive or noninvasive brain stimulation (e.g., ECT) • Sham VNS • VNS at a subtherapeutic level • No treatment	• Studies without a comparator intervention • Studies with indirect comparisons • Studies with an outdated comparator or a comparator intervention not available in the U.S.
Outcomes	• Primary outcomes: depression severity (measured using a validated tool) • Secondary outcomes: mortality; suicidal ideation and severity; response and duration of response; remission and duration of remission; treatment withdrawal; compliance with other depression treatments; anxiety (measured using a validated tool); cognitive changes (e.g., memory); quality of life (measured using a validated tool), including sleep • Safety: harms directly related to VNS (e.g., infection or hoarseness); reimplantation; failure rate • Economic: cost-effectiveness outcomes (e.g., cost per improved outcome) or cost-utility outcomes (e.g., cost per QALY, ICER)	• Other outcomes • Cost of VNS from studies performed in non-U.S. countries • Cost of VNS from studies performed in the U.S. that are older than 5 years
Setting	• Any outpatient or inpatient clinical setting in countries categorized as *very high* on the UN Human Development Index[111]	• Nonclinical settings (e.g., studies in healthy volunteers) • Countries categorized other than very high on the UN Human Development Index[111]

Study Component	Inclusion	Exclusion

Study Design	• Key Questions 1–4
	  ○ Randomized controlled trials
	  ○ Nonrandomized, comparative studies with 10 or more participants in each group
	• Additional studies/data for Key Questions 2 and 3 (harms)
	  ○ Governmental or other large, multisite registries with 100 or more participants and databases containing reports of procedure-related harms or device recalls (e.g., FDA MAUDE database, FDA Medical Device Recall database)
	• Additional studies/data for Key Question 4
	  ○ Cost-effectiveness studies and other formal comparative economic evaluations
		• Abstracts, conference proceedings, posters, editorials, letters
		• Nonrandomized, comparative studies with fewer than 10 participants in each group
		• Studies without a comparator
		• Proof-of-principle studies (e.g., technology development or technique modification)
		• Studies with harms outcomes for an intervention not included in Key Question 1
		• Registries with fewer than 100 participants

Publication	• Studies in peer-reviewed journals, technology assessments, or publicly available FDA or other U.S. government reports • Published in English • Published since June 2009 (search date in the original HTA report)	• Studies with abstracts that do not allow study characteristics to be determined • Studies that cannot be located • Duplicate publications of the same study that do not report different outcomes or follow-up times, or single site reports from published multicenter studies • Studies in languages other than English

Abbreviations. CBT: cognitive behavioral therapy; CNS: central nervous system; ECT: electroconvulsive therapy; FDA: U.S. Food and Drug Administration; HTA: Washington health technology assessment; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; TRD: treatment-resistant depression; tVNS: transcutaneous VNS; UN: United Nations; VNS: vagal nerve stimulation.

Data Sources and Searches

We conducted searches of the peer-reviewed published literature using multiple electronic databases. The time periods for searches were:

- Ovid MEDLINE and Epub Ahead of Print, In-Process & Other NonIndexed Citations and Daily: from 1946 to October 10, 2019
- Cochrane Library databases (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials): from database inception to October 10, 2019
- PsycINFO: from 1806 to October 10, 2019

Randomized controlled trials (RCTs) and systematic reviews (with and without meta-analyses) and health technology assessments that included RCTs were considered for KQs 1 to 4. Nonrandomized comparative studies and nonrandomized studies without a comparator from large, multicenter, national and international registries were considered for KQs 1 and 3 and for the harm-related aspects of KQs 2 and 3 if evidence for the intervention was included in KQ 1. For KQ 4, we also considered cost-effectiveness studies and other comparative economic evaluations, as well as systematic reviews (with and without meta-analyses) reporting economic outcomes.

The Ovid MEDLINE search strategy is shown in Appendix A. We also screened reference lists of relevant studies and used lateral search functions, such as *related articles* and *cited by*. We searched the following additional sources:

- Agency for Healthcare Research and Quality (AHRQ)
- National Institute for Health and Care Excellence (NICE) – Evidence
- Veterans Administration Evidence-based Synthesis Program

We searched these sources for systematic reviews and clinical practice guidelines using the same search terms outlined for the evidence search. In addition, we conducted a search of GuidelineCentral[112] and the Guidelines International Network guidelines library[113] in October 2019, as well as the websites of professional organizations for relevant guidelines. In these searches, we used terms related to VNS, tVNS, epilepsy, and depression and considered guidelines published in the past 5 years (January 2014 to October 2019) for inclusion. We included studies on VNS and tVNS published since the search dates of the last report (June 2009) but we did not limit by date for studies of tVNS, as this mode of VNS was not included in the original report. We also checked studies included in the original report against the inclusion/exclusion criteria for this updated report.

Using Google, we conducted a general internet search for appropriate published studies and relevant gray literature. Because of the limited reporting of harms in published studies, we also conducted a search of the U.S. FDA Manufacturer and User Facility Device Experience database (MAUDE) for VNS and tVNS. We searched for reports posted through December 2019, and the searchable database contains reports from the past 5 years. A search was also conducted of the FDA database of Medical Device Recalls, from its inception in 2002 through December 20, 2019. Findings from these searches are described in the relevant sections, and a detailed table of database reports is in Appendix G. We also searched the Medicare Coverage Database for National Coverage Determinations and Local Coverage Determinations located on the CMS's

website for literature relevant to the State of Washington. We searched the Aetna, Cigna, and Regence websites for private payer coverage policies.

To identify relevant ongoing clinical trials, in December 2019 we searched the online database of ClinicalTrials.gov maintained by the National Library of Medicine at the National Institutes of Health for terms related to VNS and tVNS. The information in this database was provided by the sponsor or principal investigator of each study. Studies are generally registered in the database when they begin and information is updated as the study progresses. We also considered studies submitted during the public comment process for possible inclusion.

Screening

We (VK and BS) independently screened titles and abstracts and reached agreement on exclusion through discussions. We performed dual full-text review for any study not excluded by review of title and abstract (Appendix J lists the excluded studies at full-text review, with reasons). For studies on which we did not agree after initial full-text review, we discussed each study and came to consensus. Any remaining disagreements were settled by a third independent researcher (CH). We also screened included references from the prior report[16] against our inclusion/exclusion criteria for this report.

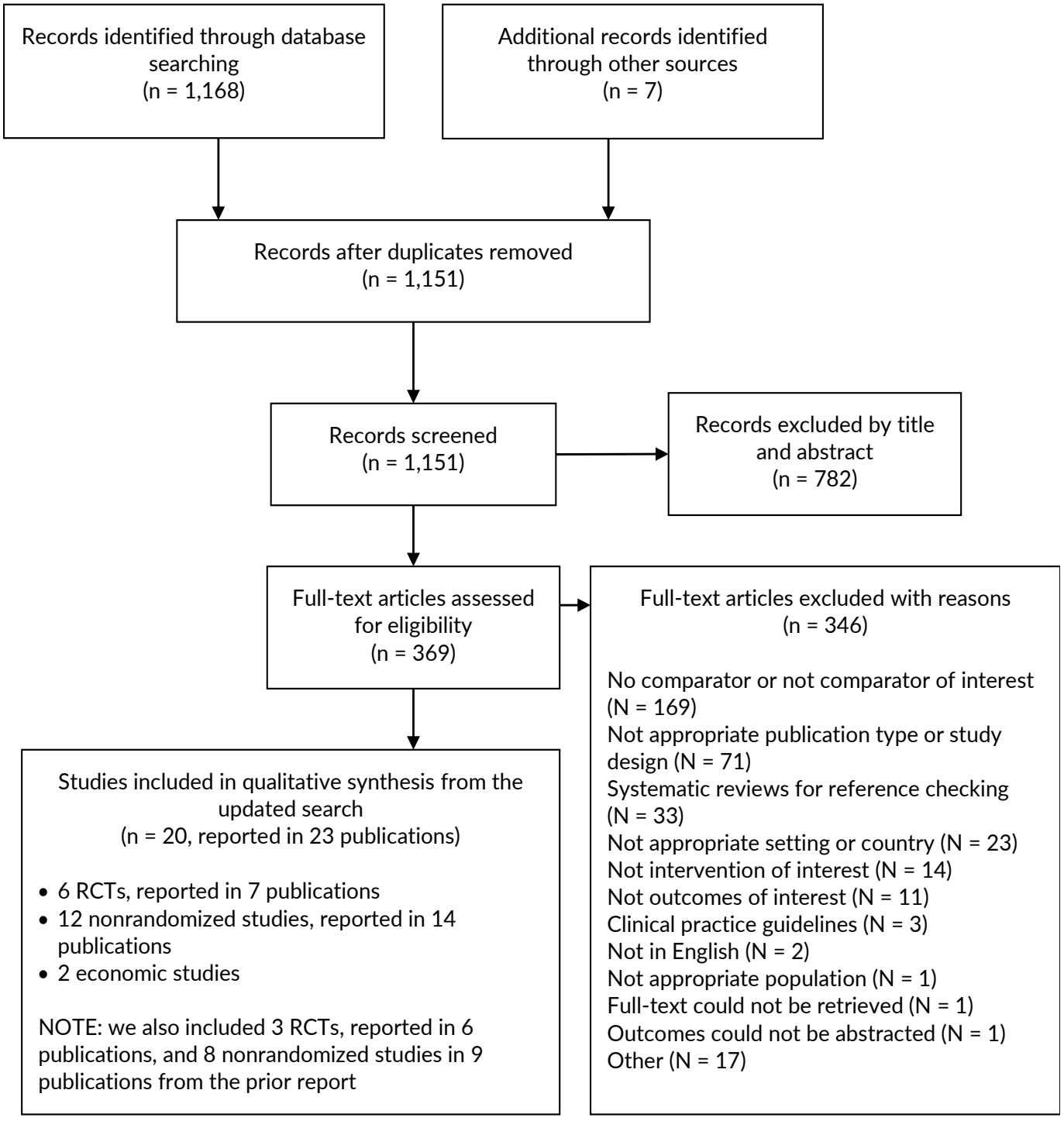

Figure 3. PRISMA Study Flow Diagram

Data Abstraction and Quality Assessment

We used standardized procedures to extract relevant data from each of the included trials and fully cross-checked all entered data for accuracy.

We (VK and BS) evaluated each eligible study for methodological risk of bias (Appendix D) and held discussions to reach agreement on these assessments. Any remaining disagreement was settled by a third independent researcher (CH). Each trial was assessed using Center instruments adapted from national and international standards and assessments for risk of bias.[114-118] A rating of high, moderate, or low risk of bias was assigned to each study based on adherence to recommended methods and the potential for internal and external biases. The risk-of-bias criteria for the study types are shown in Appendix B.

We (AV and BS) evaluated the methodological quality of eligible clinical practice guidelines. Any remaining disagreement among these assessments was settled by a third independent researcher (CH). The methodological quality of clinical practice guidelines was rated as good, fair, or poor. The assessment criteria for the methodological quality of the clinical practice guidelines are shown in Appendix B.

Data Analysis and Synthesis

We combined data in meta-analyses for the key outcomes of response (i.e., a 50% reduction in seizures and depression severity response, as defined by each specific measure) and adverse events using Review Manager.[13] For the epilepsy outcomes, we used data from the published Cochrane review[10] and planned to update the results with eligible trials, as appropriate. We did not identify any new eligible trials so were not able to update the analyses with new data. However, we amended the analyses to exclude data from the study by Michael et al.[52] as this was an interim report, with full results reported in the included study by the Vagus Nerve Stimulation Study Group.[87] We conducted sensitivity best- and worst-case analyses to account for missing outcome data, following the approach taken by the Cochrane review on VNS for partial seizures.[10] In the best-case analysis, we assumed that participants not completing follow-up or with inadequate seizure data were responders in the intervention group, and were nonresponders in the comparison group. In the worst-case analysis, we assumed that participants not completing follow-up or with inadequate seizure data were nonresponders in the intervention group, and were responders in the comparison group. We assigned selected outcomes a summary judgment for the overall quality of evidence (Appendix E) using the system developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group.[14,15] The outcomes of seizure frequency, seizure freedom, seizure severity, depression severity, suicide, response rates, withdrawals, and common adverse events (e.g., voice alteration, cough, pain) were selected from measures of effectiveness and safety. Specific measures from general domains of interest were selected in a post-hoc manner based on the outcomes available from the included studies.

The GRADE system[15] defines the overall quality of a body of evidence for an outcome in the following manner:

- **High**: Raters are very confident that the estimate of the effect of the intervention on the outcome lies close to the true effect. Typical sets of studies are RCTs with few or no limitations, and the effect estimate is likely stable.

- **Moderate**: Raters are moderately confident in the estimate of the effect of the intervention on the outcome. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is different. Typical sets of studies include RCTs with some limitations or well-performed nonrandomized studies (NRSs) with additional strengths that guard against potential bias and have large estimates of effects.
- **Low**: Raters have little confidence in the estimate of the effect of the intervention on the outcome. The true effect may be substantially different from the estimate of the effect. Typical sets of studies include RCTs with serious limitations or nonrandomized studies without special strengths.
- **Very low**: Raters have no confidence in the estimate of the effect of the intervention on the outcome. The true effect is likely to be substantially different from the estimate of the effect. Typical sets of studies include NRSs with serious limitations or inconsistent results across studies.
- **Not applicable**: Researchers did not identify any eligible articles.

Evidence Summary

Our searches returned a total of 1,168 records, published since 2009 (the search date in the prior report[16]). We also checked the reference lists of relevant systematic reviews[10,17-48] and added a further 7 studies for review.[49-55]

We found no additional studies, beyond those identified in electronic databases and reference list checking, through Google and gray literature searches. After duplicate studies were removed, 1,151 records remained (Figure 3). Of these, 369 required full-text review to determine eligibility. We also screened 71 references included in the prior report[16] against the inclusion/exclusion criteria for this report. In total, 9 RCTs (in 13 publications) and 20 NRSs (in 23 publications) met the inclusion criteria for KQs 1, 2, and 3.[49-51,55-87] In addition, 2 economics studies met the inclusion criteria for KQ 4.[88,89]

Key Questions 1 and 2

Epilepsy

We found 20 studies, reported in 23 publications, which evaluated the benefits and harms of VNS for epilepsy (Table 3 and Appendix C, Tables C1, C3 to C9, C13, C15 to C26).[49-51,55,58,60,63,64,66-69,71-73,75-77,80,82,83,86,87] We rated the risk of bias in these studies as follows:

- 2 RCTs had a moderate risk of bias due to concerns about author conflicts of interest and industry funding.
- 3 RCTs had a high risk of bias due to concerns about methodological limitations (including lack of reporting of methods and small sample sizes), early termination (of 1 trial), and industry funding.
- 1 NRS had a moderate risk of bias due to the method of analysis.
- 14 NRSs had a high risk of bias due to concerns about small sample sizes, author conflict of interest, a lack of adjustment for confounding, and patient selection.

We did not assess any of the studies as having a low risk of bias.

Table 3. Characteristics of Eligible Studies Evaluating Invasive VNS for Epilepsy

Study ID Study Risk of Bias	NCT Number/ Study Name Setting	Population	FDA-approved Indication	VNS	Comparator(s)
RCTs					
Handforth et al., 1998[80] Dodrill et al., 2001[49] Moderate	E05 20 sites in the U.S.	Adults and adolescents (aged 12 and over) with medically refractory partial-onset seizures	Yes	High-stimulation VNS[a]	Low-stimulation VNS[a]
Klinkenberg et al., 2012[82] Klinkenberg et al., 2013[83] Moderate	Not reported University medical center, Netherlands	Children and adolescents (aged 4 to 18) with medically-refractory epilepsy, and who were not eligible for surgery	Mixed	High-stimulation VNS	Low-stimulation VNS
Landy et al., 1993[51] High	Not reported University hospital, U.S.	Adults with poorly controlled complex partial seizures resistant to pharmacological treatment	Yes	High-stimulation VNS	Low-stimulation VNS
Ryvlin et al., 2014[86] High	NCT00522418 PuLsE 28 sites in Europe and Canada	Adults and adolescents (aged 16 and over) with medically-refractory focal seizures	Yes	VNS with best medical practice	Best medical practice
Vagus Nerve Stimulation Group, 1995[87] Elger et al., 2000[50] High	E03 17 sites in the U.S., Canada, and Europe	Adults and adolescents (aged 12 and over) with medically intractable partial seizures	Yes	High-stimulation VNS	Low-stimulation VNS
Nonrandomized Studies and Registry-based Studies					
Boon et al., 2002[58] High	Not reported University hospital, Belgium	Adults and adolescents (aged 12 and over) with refractory epilepsy, undergoing presurgical assessment	No	VNS	Continued medication Epilepsy surgery
Ellens et al., 2018[60] High	Not reported Not clear, U.S.	Adults and children (aged under 18) with medically intractable epilepsy secondary to complex partial seizures	Yes	VNS	Responsive neurostimulation

Study ID Study Risk of Bias	NCT Number/ Study Name Setting	Population	FDA-approved Indication	VNS	Comparator(s)
Gonen et al., 2015[63] High	Not reported Medical center, Israel	Adults with refractory epilepsy	Yes	VNS	Continued medication
Harden et al., 2000[64] High	Not reported University hospital, U.S.	Adults with VNS for seizure control	Mixed	VNS	Continued medication
Hoppe et al., 2013[66] High	Not reported Not clear, Germany	Adults with refractory epilepsy	Mixed	VNS	Best available drug treatment (after a failed presurgical evaluation)
Jamy et al., 2019[67] High	Not reported Neuromodulation clinic, U.S.	Adults with drug-resistant epilepsy	No	VNS	Responsive neurostimulation
Kawai et al., 2017[68] Moderate	Not reported National registry, Japan	Adults and children (aged 1 and over) with drug-resistant epilepsy	No	VNS	No comparator (included for harms only)
Kuba et al., 2013[69] High	Not reported University medical center, Czechia	Adults with nonlesional extratemporal epilepsy	No	VNS	Surgery
McGlone et al., 2008[71] High	Not reported Not clear, Canada	Adults and adolescents (aged 16 and over) with medically-refractory complex partial seizures	Yes	VNS	Surgery Medication
Morrison-Levy et al., 2018[72] High	Not reported Tertiary center, Canada	Children (aged 1 to 18) with autism spectrum disorders and drug-resistant epilepsy	No	VNS	Surgery
Nei et al., 2006[73] High	Not reported Epilepsy center, U.S.	Adults and adolescents (aged 13 and over) with refractory epilepsy	No	VNS	Corpus callosotomy
Ryvlin et al., 2018[75] High	Not reported National registry, U.S.	Adults and children of any age with epilepsy	No	VNS	No comparator (included for harms only)
Sherman et al., 2008[76] High	Not reported Tertiary pediatric hospital, Canada	Children (aged 3 to 18) with intractable epilepsy	No	VNS	No VNS

Study ID Study Risk of Bias	NCT Number/ Study Name Setting	Population	FDA-approved Indication	VNS	Comparator(s)
Van Lierde et al., 2015[77] High	Not reported University hospital, Belgium	Adults with epilepsy	Not clear	VNS	No VNS
You et al., 2008[55] High	Not reported Epilepsy centers, Korea	Children (age not specified) with Lennox–Gastaut syndrome	No	VNS	Corpus callosotomy

Note. [a] Studies often compared a therapeutic level of VNS, following a high-stimulation protocol, with VNS at a subtherapeutic level, following a low simulation protocol. Abbreviations. FDA: U.S. Food and Drug Administration; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; VNS: vagal nerve stimulation.

We also found 1 RCT that evaluated the benefits and harms of tVNS for epilepsy (Table 4 and Appendix C, Tables C1 and C3).[79] We rated the risk of bias of this study as high because of concerns about a lack of reporting of methods, the high loss to follow-up, and conflicts of interest were not reported.

Table 4. Characteristics of Eligible Studies Evaluating Transcutaneous VNS for Epilepsy

Study ID Study Risk of Bias	NCT Number/ Study Name Setting	Population	FDA-approved Indication	tVNS	Comparator
RCTs					
Bauer et al., 2016[79] High	cMPsE02 9 sites in Germany and 1 site in Austria	Adults with drug-resistant epilepsy	No	High-stimulation tVNS	Low-stimulation tVNS

Abbreviations. FDA: U.S. Food and Drug Administration; NCT: U.S. National Clinical Trial number; RCT: randomized controlled trial; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

Study Characteristics

The majority of RCTs of VNS in people with epilepsy (4 of 5 studies) included children or adolescents with epilepsy.[80,82,86,87] Most of the trials were multicenter trials across U.S., Canada and Europe,[64,86,87] with only 2 trials being conducted in single centers (1 in the U.S. and 1 in the Netherlands).[51,82] The majority of studies included people with medically refractory partial seizures,[51,80,86,87] with 1 RCT including children with medically-refractory epilepsy who were not eligible for surgery.[82] Most of the trials compared a high-stimulation VNS protocol (i.e., VNS at a therapeutic level) with a low-stimulation VNS protocol (i.e., VNS at a subtherapeutic level), in order to preserve blinding in both the participants and the investigators.[51,80,82,87] The stimulation protocols used in the 4 RCTs were similar (Table 5).[51,80,82,87] Only 1 trial compared VNS with best medical practice.[86]

Table 5. VNS Parameters in Studies Comparing High- vs. Low-stimulation VNS for Epilepsy

VNS Stimulation Parameter	Handforth et al., 1998[80]		Klinkenberg et al., 2013[83]		Landy et al., 1993[51]		Vagus Nerve Stimulation Group, 1995[87]	
	High	Low	High	Low	High	Low	High	Low
Current (mA)	Mean 1.3	Mean 1.2	0.25	0.25	0.5 to 3.0 (maximum tolerable)	0.5 to 3.0 (minimum response)	0.25 to 3.0	0.25 to 2.75
Frequency (Hz)	30	1	30	1	20 to 50	1 to 2	20 to 50	1 to 2
Pulse Width (µsec)	500	130	500	130	500	130	500	130
On Time (seconds)	30	30	30	14	30 to 90	30	30 to 90	30
Off Time (minutes)	5	5	5	60	5 to 10	60 to 180	5 to 10	60 to 180
Manual Activation Mode	Enabled	Disabled	NR	NR	Enabled	Disabled	Enabled	Disabled

Abbreviations. µsec: microsecond; Hz: Hertz; mA: milliamp; NR: not reported; VNS: vagal nerve stimulation.

The RCT evaluating tVNS compared a high-stimulation VNS protocol with a low-stimulation VNS protocol (Table 6).[79] The RCT included only adults with drug-resistant epilepsy and was conducted at sites in Germany and Austria.

Table 6. VNS Parameters in Studies Comparing High- vs. Low-stimulation tVNS for Epilepsy

tVNS Stimulation Parameter	Bauer et al., 2016[79]	
	High	Low
Current (mA)	NR	NR
Frequency (Hz)	25	1
Pulse Width (µsec)	250	NR
On Time	30 seconds	NR
Off Time	30 seconds	NR
Manual Activation Mode	NR	NR

Abbreviations. µsec: microsecond; Hz: Hertz; mA: milliamp; NR: not reported; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

The majority of the NRSs (9 of 15 studies) included children or adolescents,[55,58,60,68,71-73,75,76] with 3 of the 9 studies including only children.[55,72,76] The NRSs tended to include a wider range of epilepsies and seizures than RCTs. For example, Jamy et al.[67] and Morrison-Levy et al.[72] included adults and children with drug-resistant epilepsy of any type. Similarly, the comparators were more varied, with studies comparing VNS with ongoing medication,[58,63,64,66,71] surgery,[55,58,69,71-73] responsive neurostimulation, [60,67] and no VNS.[77] We also included 2 registry studies reporting harms.[68,76] Most of the eligible NRSs were conducted in the U.S.[26,64,67,73,75] or Europe,[58,66,69,77] with a further 3 studies in Canada,[71,72,76] and 1 study each in Israel,[63] Japan,[68] and Korea.[55]

Study Findings

Seizure Frequency

We identified 5 eligible RCTs[51,80,82,86,87] and 10 eligible NRSs[55,58,60,63,64,66,67,69,72,73] reporting seizure frequency.

High-stimulation VNS was associated with higher rates of response, defined as a reduction of 50% or more in seizures, compared with low-stimulation VNS (Figure 4). However, the summary estimate was sensitive to missing data, with a worst-case analysis showing no significant difference, although the effect estimate is similar (risk ratio [RR], 1.51; 95% confidence interval [CI], 0.99 to 2.29; Appendix F).

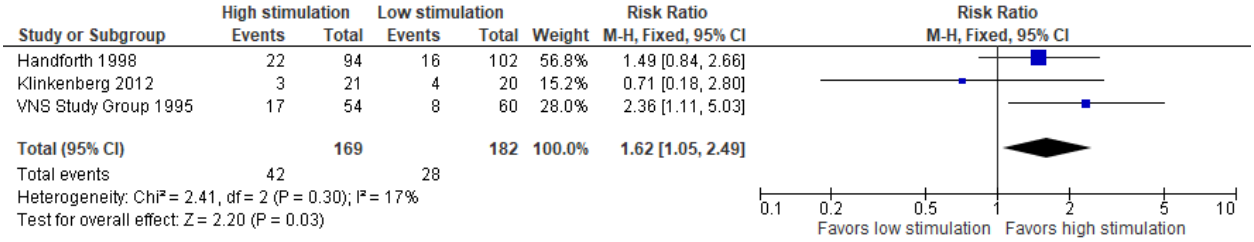

Figure 4. VNS High- vs. Low-stimulation, Outcome: 50% Responders

In the RCT by Landy et al.,[51] high-stimulation VNS was also associated with a reduction in number of seizures when compared with low-stimulation VNS over the 12 to 17 weeks of blinded treatment (Figure 5).

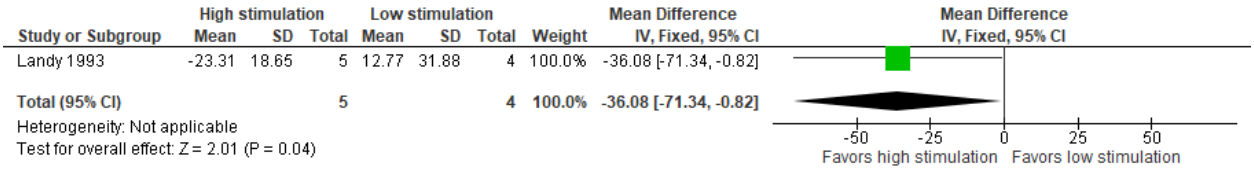

Figure 5. VNS High- vs. Low-stimulation, Outcome: Change in Seizure Frequency

When compared with ongoing medical treatment, VNS was not associated with a greater response rate (Figure 6).[86] However, VNS was associated with a greater reduction in number of seizures per week over 12 months than medication alone (details not reported; *P* = .03). The results were highly sensitive to missing data, with the worst-case analysis supporting treatment as usual (TAU), rather than VNS (RR, 0.41; 95% CI, 0.22 to 0.77; Appendix F).

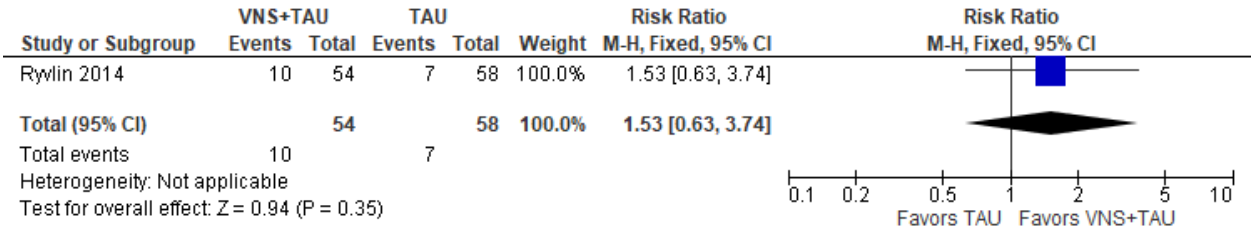

Figure 6. VNS vs. Treatment as Usual, Outcome: 50% Responders

The results from the NRSs also supported the effectiveness of VNS on seizure frequency when compared with AEDs.

- Boon et al. [58] found that individuals in the VNS group had greater reductions in seizure frequency than those in the medication group (change in complex partial seizures of 21 per month to 7 per month in the VNS group, vs. 12 per month to 9 per month in the medication group; *P* = .002).
- In the study by Gonen et al.,[63] participants in the VNS and the medication groups showed significant reductions in seizure frequency after treatment (reduction in seizure frequency from 3.52 to 2.94 in the VNS group; *P* = .006; reduction in seizure frequency of 3.15 to 2.38 in the medication group; *P* < .001).[63] However, the mean seizure frequency was higher in the VNS group compared with medication alone (2.94 vs. 2.38; *P* = .047).[63]
- Harden et al.[64] reported that participants in the VNS group had a significant decrease in seizure frequency compared with the medication group (mean change in seizures per month of 16.2 to 8.9 in the VNS group vs. 3.2 to 2.0 in the medication group; *P* = .01).
- Hoppe et al.[66] found that participants in the VNS group had greater response rates (> 50% response, 12 of 20 vs. 7 of 20) than participants in the medication group, with higher rates of seizures worsening in the medication group (10% vs. 40%; *P* = .004).

When compared with surgery, VNS was also associated with improvements in seizure frequency, although results were not consistent across studies.

- Kuba et al. [69] found that VNS and surgery were associated with fewer seizures at 2 and 5 years (change in mean number of seizures per month from 58.4 to 28.7 at 2 years and 27.4 at 5 years in the VNS group, vs. 78.8 to 27.4 at 2 years and 22.6 at 5 years in the surgery group; *P* < .001 over time); however, there was no significant differences between groups (at 2 years, *P* = .22; at 5 years, *P* = .22).
- You et al.[55] found similar rates of response (defined as a reduction in seizures of 50% or more) in the VNS and surgery groups (70.0% vs. 64.3%; *P* > .05).
- Morrison-Levy et al.[72] reported that surgery was associated with greater reductions in seizures (defined as Engel classes I [seizure free], II [rare disabling seizures], and III [a worthwhile improvement]) than VNS (50% of participants in the VNS group compared with 80% of participants in the surgery group), with fewer people in the surgery group having no meaningful reduction (50% of participants in the VNS group compared with 20% of participants in the surgery group categorized as Engel class IV). The difference between groups was not statistically significant (*P* = .13).[72]
- Nei et al.[73] also found that corpus callosotomy resulted in greater reductions in seizure frequency than VNS, with 40% of participants in the VNS having a reduction in seizures of 50% or more compared with 79% in the surgery group (*P* < .001).

When compared with responsive neurostimulation, Ellens et al.[60] found that VNS and responsive neurostimulation were associated with similar number of seizures per month (median number of seizures, 1.3 vs. 2.5; *P* = .58) and similar reductions after treatment (reduction in seizures, 66% vs. 58%; *P* = .87). Jamy et al.[67] found that VNS was associated with a 44% response rate (defined as a 60% or more reduction in seizures) compared with a 69% response rate for responsive neurostimulation (*P* value not reported). The rates of nonresponse, defined as a

change in seizure frequency of less than 30%, were 15% in the VNS group and 6% in the responsive neurostimulation (*P* value not reported).[67]

Seizure Freedom

We identified 2 eligible RCTs[80,87] and 10 eligible NRSs[55,58,60,63,64,66,67,69,72,73] reporting seizure freedom.

Across both RCTs, only 1 participant receiving high-stimulation VNS and no participants in the low-stimulation groups became seizure-free.[80,87] The NRSs also showed very low rates of seizure freedom. In the 4 studies comparing VNS with ongoing medication:

- In the study by Boon et al.,[58] 6 of the 25 participants in the VNS group became free of complex partial seizures, with 3 continuing to have simple partial seizures, compared with 1 of the 24 participants in the medication group.
- No individuals in either the VNS group or the medication group became seizure-free in the study by Gonen et al.[63]
- In the study by Harden et al.,[64] 1 of 20 participants in the VNS group became seizure-free, compared with 2 of 20 participants in the medication group.
- Hoppe et al.,[66] reported that 1 of the 20 participants in the VNS group was seizure-free, compared with 4 of 20 participants in the medication group.

In the 5 NRSs comparing VNS with surgery:

- In the study by Boon et al.,[58] 6 of the 25 (24%) participants in the VNS group became free of complex partial seizures, with 3 continuing to have simple partial seizures, compared with 23 of the 35 (65.7%) participants in the surgical group being free of complex partial seizures.
- Morrison-Levy et al.[72] reported that no patients in the VNS group became seizure-free compared to 10 of the 15 (66.7%) patients in the surgery group. When compared with the numbers of participants who did not become seizure-free, surgery was more effective than VNS (P < .001).[72]
- In the study by Kuba et al.,[69] participants in the surgical group had higher rates of seizures freedom than those in the VNS group (23.1% vs. 5.8%; *P* = .04)
- No patients in the VNS group became seizure-free compared with 9 patients who achieved this in the corpus callosotomy group.[73]
- You et al.[55] reported that in the VNS group, 2 of 10 became seizure-free compared with 4 of 14 in the corpus callosotomy group. The difference between groups was not statistically significant (*P* = .51).[55]

In the 2 NRSs comparing VNS with responsive neurostimulation:

- Ellens et al.[60] found no significant difference in the rates of seizure freedom (15.4% vs. 23.5%; *P* = .67).
- In the study by Jamy et al.,[67] no patients (0 of 27) in the VNS group became seizure-free, compared with 4 of the 16 (25%) patients in the responsive neurostimulation group.

Seizure Severity

We identified 1 eligible RCT comparing high- and low-stimulation VNS in children reporting seizure severity using a validated scale.[82] Severity was measured using the adapted Chalfont

Seizure Severity Scale (NHS3) which includes 7 seizure-related factors and generates a score from 1 to 27.[82] The higher the NHS3 score, the more severe the seizures.[82] At 20 weeks, seizure severity was similar in the high-stimulation and low-stimulation groups (mean change in NHS3 score, -0.3, high-stimulation vs. -0.6, low-stimulation; *P* = .71).[82]

Seizure Duration

We did not identify any eligible studies reporting seizure duration.

Treatment Withdrawal

We identified 4 eligible RCTs[80,82,86,87] reporting withdrawals. VNS was not associated with higher levels of withdrawals in the RCTs comparing high- and low-stimulation VNS or comparing VNS with TAU (Figure 7 and Figure 8).

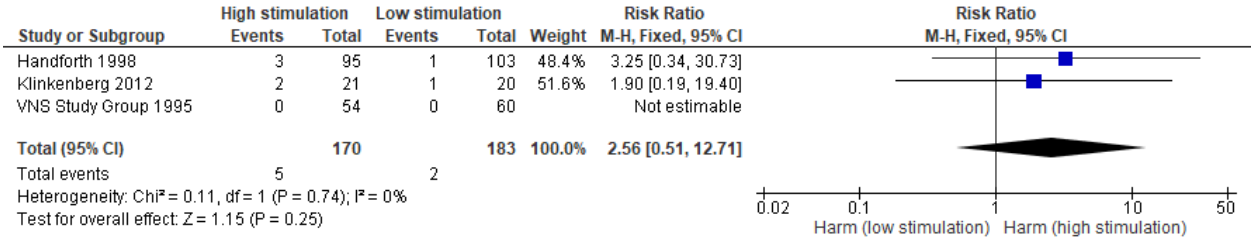

Figure 7. VNS High- vs. Low-stimulation, Outcome: Withdrawals

Figure 8. VNS vs. Treatment as Usual, Outcome: Withdrawals

Mood or Cognitive Changes

We identified 4 eligible RCTs[49,50,80,82,83,86,87] and 3 eligible NRSs[64,66,71] reporting measures of mood or cognitive changes. In 2 RCTs comparing high- and low-stimulation VNS, participants in both groups had similar levels of cognitive task performance (e.g., verbal reasoning, math, and logic skills)[49,80] and other measures of cognition, mood, epilepsy-related restrictions or psychosocial adjustment.[82,83] Klinkenberg et al.[82,83] evaluated the longer-term use of VNS in an add-on phase to the randomized phase, where all children received high-stimulation VNS. At the end of the 19-week add-on phase, children experienced a significant improvement in depression (*P* = .03) from baseline but not in cognition, total mood disturbance, epilepsy-related restrictions, or psychosocial adjustment.[82,83] Elger et al.[50] reported on a subset of patients with more than 4 medication-resistant complex-partial seizures before implantation from the E03 study.[87] The 11 participants experienced significant positive mood effects at 3 months (*P* < .05), which were independent of the effects of VNS on seizure response, and the improvements were sustained at

6 months.[50] In the RCT by Ryvlin et al.,[86] participants in both the VNS and best-medical-treatment groups had similar levels of depression at 12 months ($P > .05$).

In the NRS by Harden et al.,[64] participants in the VNS group and the AED group had similar levels of depression and anxiety at follow-up. Similarly, Hoppe et al.[66] found that there were no significant differences between the VNS group and the AED group on most measures of depression and other psychosocial outcomes, although participants in the VNS group reported higher rates of anxiety (50% vs. 20%; $P = .047$)

In the study by McGlone et al.,[71] comparing VNS and surgery, participants in both groups had similar memory function and depression scores at 12 months ($P > .05$).

Quality of Life

We identified 2 eligible RCTs[49,80,86] and 4 eligible NRSs[66,71,76,77] reporting quality of life. In the high- and low-stimulation groups, patient, interviewer, and companion ratings of patient well-being were higher at the end of treatment than at baseline ($P < .001$), and although the patient and interviewer ratings of well-being were higher in the high-stimulation group it is not clear if the differences were clinically meaningful.[80] Patients in the high-stimulation group also had fewer emotional and physical problems after treatment, with responders having slightly more improvement in quality of life (a reduction of 50% or more in seizure frequency) than nonresponders.[49] When compared with best medical treatment, participants in the VNS group had a higher quality of life, as measured using the Quality of Life in Epilepsy Inventory-89 (QOLIE-89) (3.1 vs. 0.6; $P < .05$), but the clinical importance of this difference is uncertain.[86]

In the 2 NRSs comparing VNS with pharmacological treatment:

- Patients in both groups had similar levels of quality of life and psychosocial status on most measures, although participants in the VNS group reported higher satisfaction with their living conditions (scored from 0 [very low] to 5 [very high]; 4.1 vs. 3.1; $P = .04$)[66]
- In the study by Sherman et al.,[76] participants in the VNS group reported a better mean epilepsy-related and global quality of life ($P < .05$) compared with AEDs. However, when the proportions of children who reported worsened, unchanged, or improved quality of life were compared, there were no significant differences between the groups ($P > .05$).[76]

When compared with surgery, participants in the VNS and surgery groups had similar levels of quality of life ($P > .05$), although patients in the surgery group did have a significantly higher self-reported quality of life than the VNS group.[71]

One study assessed the impact of VNS-related vocal problems on quality of life.[77] Participants in the VNS group reported a significantly higher impact of vocal problems on physical, functional, and emotional quality of life than people in the no-VNS group ($P < .05$).[77]

Harms

We identified 4 eligible RCTs[80,82,86,87] and 7 eligible NRSs[55,60,67,68,73,75,77] reporting VNS-related harms or adverse events. Based on our meta-analysis of 2 RCTs comparing high- and low-stimulation VNS,[80,87] patients in the high-stimulation group had higher rates of voice alteration or hoarseness, dyspnea but not cough, pain, paresthesias, nausea or headache (Figures 9 to 15).

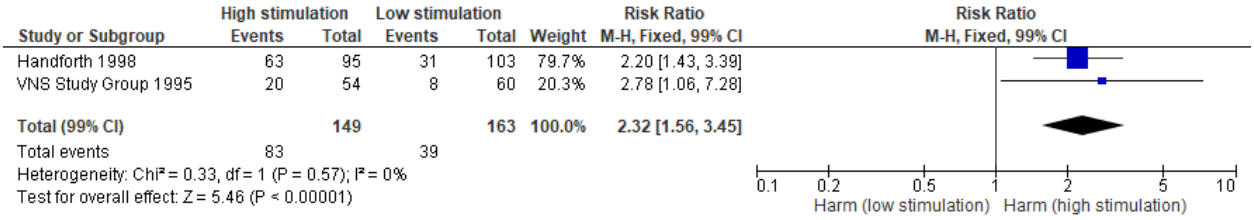

Figure 9. VNS High- vs. Low-stimulation, Outcome: Voice Alteration or Hoarseness.

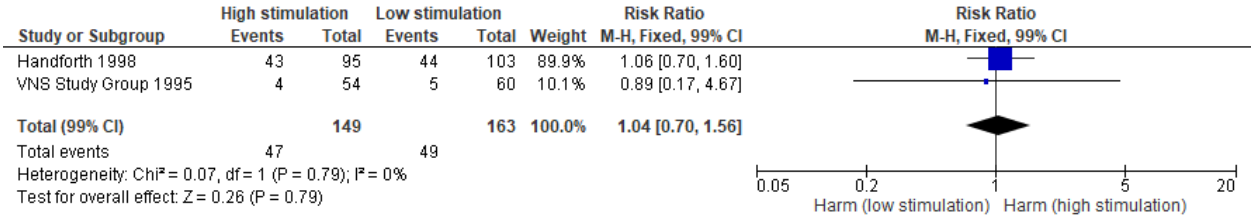

Figure 10. VNS High- vs. Low-stimulation, Outcome: Cough

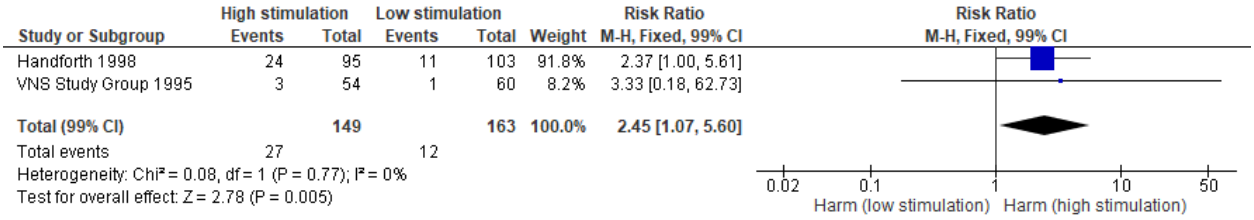

Figure 11. VNS High- vs. Low-stimulation, Outcome: Dyspnea

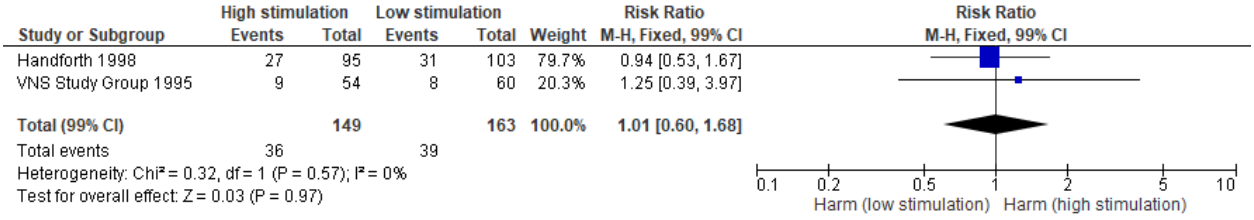

Figure 12. VNS High- vs. Low-stimulation, Outcome: Pain

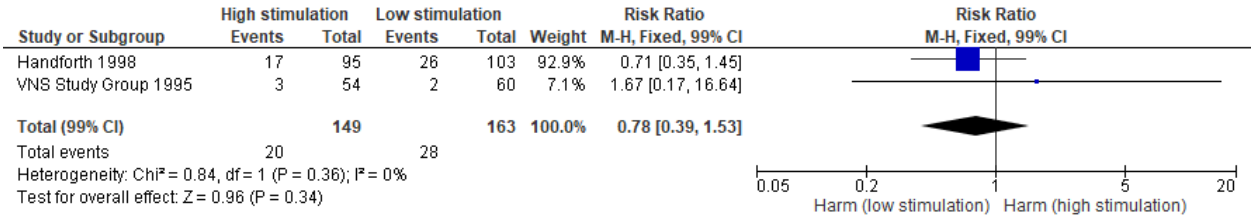

Figure 13. VNS High- vs. Low-stimulation, Outcome: Paresthesias

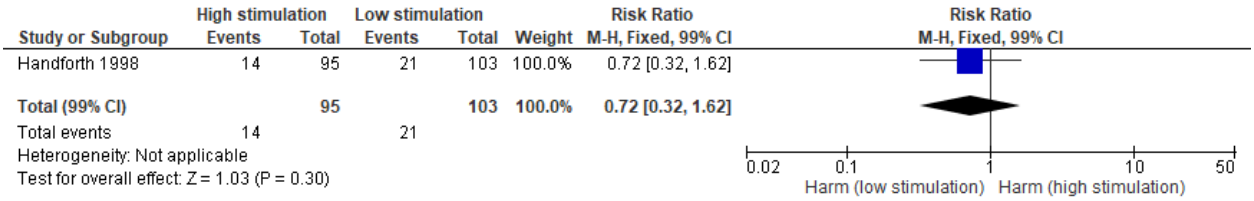

Figure 14. VNS High- vs. Low-stimulation, Outcome: Nausea

Figure 15. VNS High- vs. Low-stimulation, Outcome: Headache

Children in the RCT by Klinkenberg et al.[82] experienced similar adverse events, but these were not reported by level of VNS stimulation. Children also experienced behavioral changes, including agitation, crying, and frequent startles.[82]

Compared with TAU, Ryvlin et al.[86] found that VNS was associated with similar rates of voice alteration or hoarseness, pain, paresthesias, and headache (Figures 16 to 19). Other adverse events, specifically cough, dyspnea, nausea were not reported.[86]

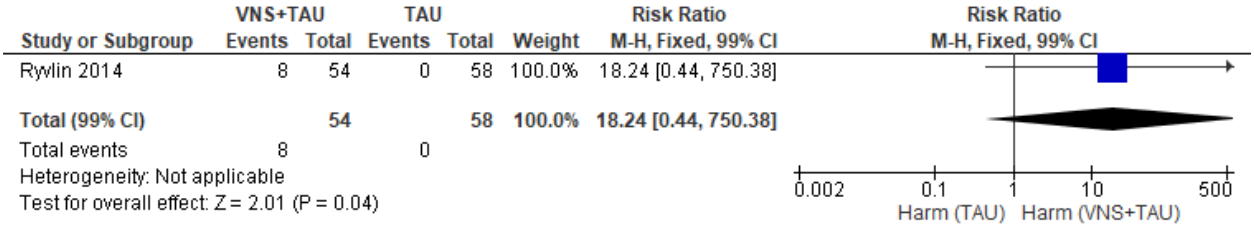

Figure 16. VNS vs. Treatment as Usual, Outcome: Voice Alteration or Hoarseness

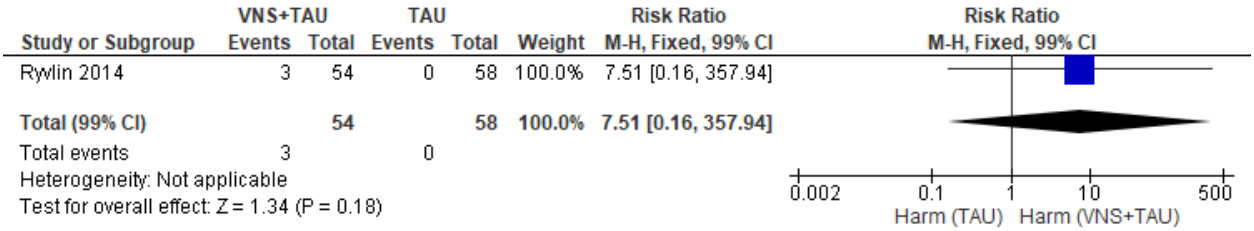

Figure 17. VNS vs. Treatment as Usual, Outcome: Pain

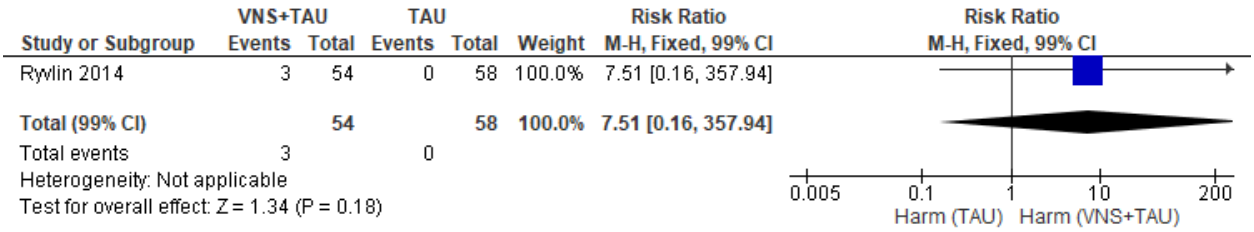

Figure 18. VNS vs. Treatment as Usual, Outcome: Paresthesias

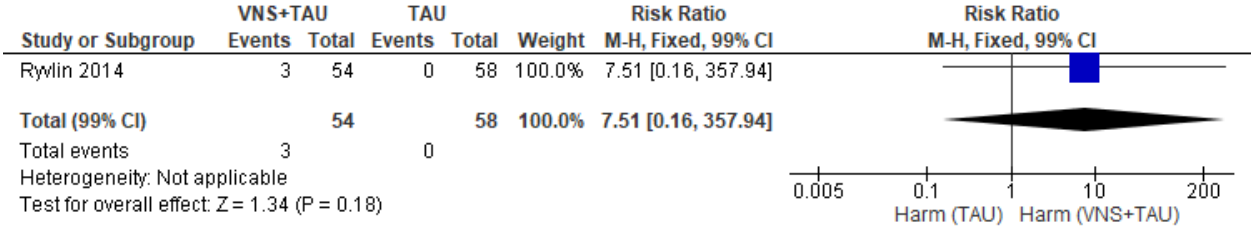

Figure 19. VNS vs. Treatment as Usual, Outcome: Headache

We identified 2 large registries reporting on VNS-related harms:

- Kawai et al.[68] found that rates of laryngeal symptoms (including hoarseness and coughing) and local dysesthesias tended to decrease over time (laryngeal symptoms, 11.2% to 4.5% at 36 months; dysesthesias, 1.6% to 0.3% at 36 months) while rates of high lead impedance tended to increase (0.3% to 3.0% at 36 months). Other adverse events, such as cardiac or respiratory complications and local infections, were low at all-time points (0.3% to 0.6%).[68]
- Kawai et al.[68] also reported 14 deaths, of which 6 were SUDEP, 3 cancer- or tumor-related, 1 pneumonia, 1 subarachnoid hemorrhage, 1 drowning while bathing, and 1 seizure-related suffocation. The cause of death for 1 participant was not reported.[68]
- In the study by Ryvlin et al.,[75] 3,689 of 40,433 patients (9%) died. The all-cause mortality rate was 13.3 per 1,000 person-years (95% CI, 12.9 to 13.7), with an age- and gender-adjusted standardized mortality rate of 4.58 (95% CI, 4.43 to 4.73).[75] Of the 3,689 who died, 632 were SUDEP, with 38 (4%) classified as definite SUDEP, 63 (7%) as probable SUDEP, and 531 (56%) as possible SUDEP.[75]

Van Lierde et al.[77] found that participants in the VNS group were assessed as having significantly more hoarseness, roughness, breathiness, and strained vocal characteristics than participants in the no-VNS group.

Nei et al.[73] compared VNS and corpus callosotomy in 61 patients. In the VNS group, no patients died compared with 6 patients in the surgery group (1 in the immediate post-operative period, 4 of SUDEP, and 1 of pneumonia). Complication rates were also higher in the surgery group (8% vs. 21%).[73] However, complications in the VNS group (1 site infection, 1 defective battery) tended to be less serious than those in the corpus callosotomy group (1 death, 1 status epilepticus, 1 infection, 3 hemiparesis, 2 gait difficulty, 2 disconnection syndrome, and 1 deep venous thrombosis).[73] Most of the complications in the VNS groups resolved or improved, compared with 3.5% of complications in the corpus callosotomy group.[73]

You et al.[55] evaluated VNS and surgery in children with Lennox-Gastaut syndrome. In the VNS group, 2 of 10 (20%) had complications (dyspnea during sleep in 1 patient and drooling in 1 patient). The complications were transient and tolerable and could be controlled by simple adjustment of VNS parameters.[55] In the corpus callosotomy group, observed complications were aphasia in 1 patient, ataxia in 1 patient, and paresis in 1 patient.[55] There was no significant differences in complication rates between VNS and surgery (P = .39).[55]

Ellens et al.[60] reported similar levels of total complications with VNS and responsive neurostimulation, with 2 patients in the VNS group experiencing temporary hoarseness. In the study by Jamy et al.,[67] 41% of patients in the VNS group experienced transient increases in coughing and hoarseness. One patient in the VNS group had symptomatic partial vocal cord paralysis, and the device was turned off.[67]

Reimplantation

We identified 1 eligible RCT[80] and 1 eligible NRS[67] reporting reimplantation rates. In the RCT, of the 3 devices removed after infection, 1 was reimplanted during the study.[80] In the study by Jamy et al.[67] 7 of 27 patients (25%) had a new implant during the study period.

Failure Rate

We identified 3 eligible RCTs[51,80,87] and 3 eligible NRSs[67,68,75] reporting failure rates.

Handforth et al.[80] reported that of the 3 devices removed after infection, 1 was reimplanted during the study and that no devices malfunctioned.

- VNS devices remained in place for periods of 6 to 13 months with no further delayed complications in the RCT by Landy et al.[51]
- In the Vagus Nerve Stimulation Study, 2 signal generators malfunctioned, resulting in 1 case of ongoing vocal cord paralysis.[87] There were no cases of intrinsic wire lead or electrode failure, and reoperation was required in 1 case of lead detachment.[87]
- In the study by Kawai et al.[68] 13 of 385 patients (3.4%) had the VNS explanted (6 because of infection, 6 with high lead impedance, and 1 for a magnetic resonance imaging scan).
- Ryvlin et al.[75] reported that 2,864 of 40,433 (7%) had the VNS device explanted or turned off.

Transcutaneous VNS

We identified 1 eligible RCT comparing high- and low-stimulation tVNS.[79] Participants in both groups had similar rates of response (defined as a 50% or greater reduction in seizure frequency; Figure 20), seizure freedom (2.6% vs. 7.7%; no P value reported), and similar seizure severity scores (a change of 1.56 vs. 0.83; P > .05).[79] The number of withdrawals was also similar between the high- and low-stimulation groups (Figure 21).[79] Patients in both groups had similar levels of depression and quality of life scores).[79] Rates of pain, nausea, and headache were not significantly different between the groups (Figures 22 to 24) and participants did not report any adverse events of coughing or voice alteration.[79] There was 1 SUDEP in the low-stimulation group, but this was assessed as not being related to treatment.[79]

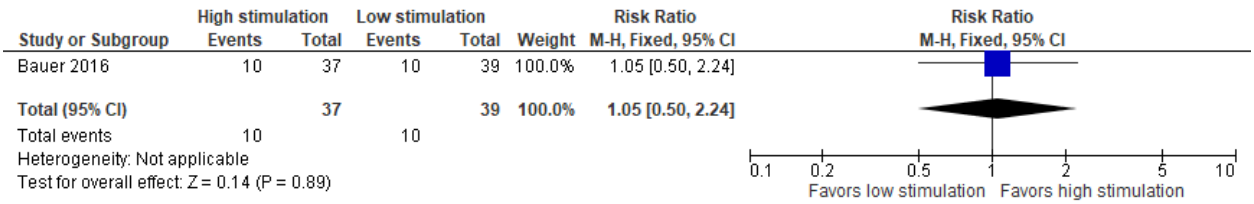

Figure 20. tVNS High- vs. Low-stimulation, Outcome: 50% responders

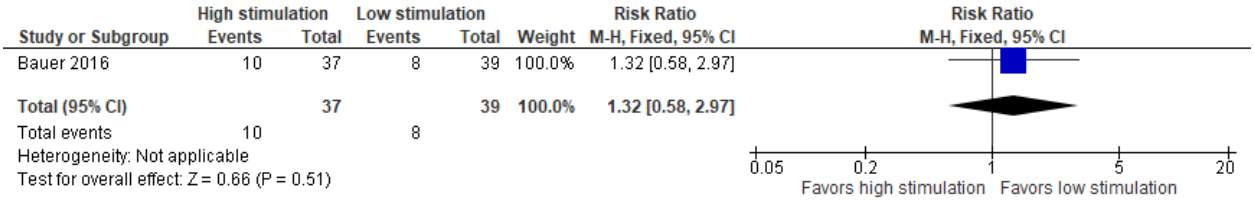

Figure 21. tVNS High- vs. Low-stimulation, Outcome: Withdrawals

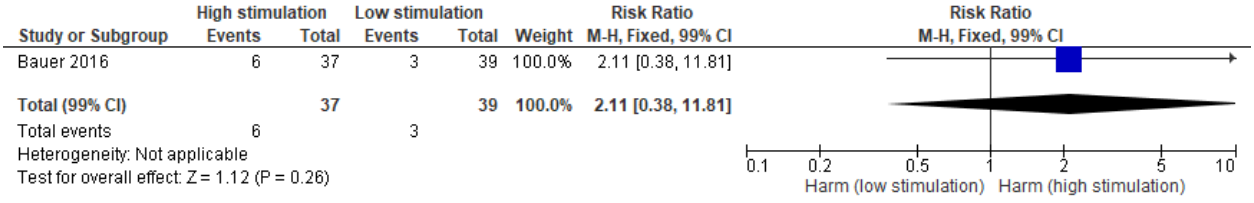

Figure 22. tVNS High- vs. Low-stimulation, Outcome: Pain

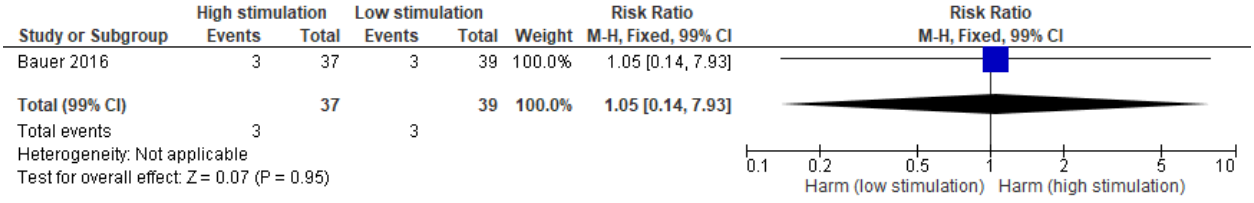

Figure 23. tVNS High- vs. Low-stimulation, Outcome: Nausea

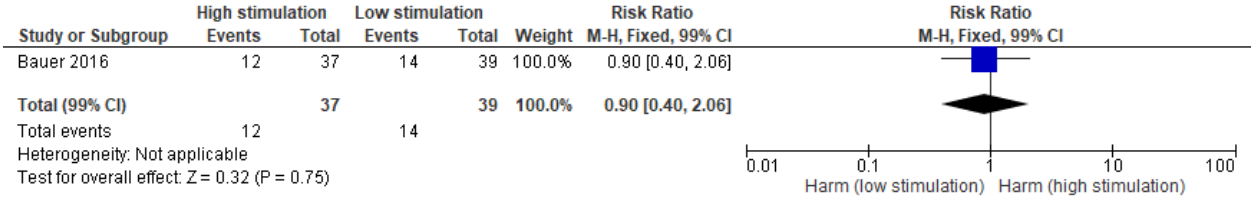

Figure 24. tVNS High- vs. Low-stimulation, Outcome: Headache

GRADE Summary of Findings

Table 7. GRADE Summary of Evidence: Effectiveness of VNS in Epilepsy

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
High-stimulation VNS vs. Low-stimulation VNS			
Outcome: Reduction of 50% or More in Seizure Frequency			
N = 351 3 RCTs[80,82,87]	RR, 1.62; 95% CI, 1.05 to 2.49	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Mean Change in Seizure Frequency			
N = 9 1 RCT[51]	MD, -36.08; 95% CI, -71.34 to -0.82	⨁◯◯◯ VERY LOW	Downgraded 2 levels for risk of bias, and 1 level for imprecision (i.e., wide CIs)
Outcome: Seizure Freedom			
N = 312 2 RCTs[80,87]	1 participant receiving high-stimulation VNS and no participants in the low-stimulation groups became seizure-free	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
VNS vs. Treatment as Usual or Ongoing Medication			
Outcome: Reduction of 50% or More in Seizure Frequency			
N = 112 1 RCT[86]	RR, 1.53; 95% CI, 0.63 to 3.74	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., wide CIs)
Outcome: Seizure Frequency (various measures)			
N = 216 4 NRSs[58,63,64,66]	VNS is associated with greater improvements in seizure frequency than treatment as usual or ongoing medication	⨁◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Seizure Freedom			
N = 216 4 NRSs[58,63,64,66]	VNS does not appear to be associated with higher rates of seizure freedom than treatment as usual or ongoing medication	⨁◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
VNS vs. Surgery			
Outcome: Seizure Frequency (various measures)			
N = 192 4 NRSs[55,69,72,73]	VNS may be associated with similar improvements in seizure frequency than surgery, but surgery may be more effective for some patients or specific epilepsies	⨁◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
Outcome: Seizure Freedom			
N = 252 5 NRSs[55,58,69,72,73]	Surgery may be associated with higher rates of seizure freedom than VNS, but results are not consistent	⨁◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)
VNS vs. Responsive Neurostimulation			
Outcome: Seizure Frequency (various measures)			
N = 73 2 NRSs[60,67]	VNS may be associated with similar improvements in seizure frequency than responsive neurostimulation, but results are not consistent	⨁◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)
Outcome: Seizure Freedom			
N = 73 2 NRSs[60,67]	VNS may be associated with similar rates of seizure freedom than responsive neurostimulation, but results are not consistent	⨁◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)

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

Table 8. GRADE Summary of Evidence: Harms of VNS in Epilepsy

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

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
Outcome: Cough			
N = 312 2 RCTs[80,87]	RR, 1.04; 95% CI, 0.70 to 1.56	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Dyspnea			
N = 312 2 RCTs[80,87]	RR, 2.45; 95% CI, 1.07 to 5.60	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Pain			
N = 312 2 RCTs[80,87]	RR, 1.01; 95% CI, 0.60 to 1.68	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Paresthesias			
N = 312 2 RCTs[80,87]	RR, 0.78; 95% CI, 0.39 to 1.53	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Nausea			
N = 312 2 RCTs[80,87]	RR, 0.72; 95% CI, 0.32 to 1.62	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Headache			
N = 312 2 RCTs[80,87]	RR, 0.90; 95% CI, 0.48 to 1.69	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
VNS vs. Treatment as Usual			
Outcome: Treatment Withdrawals			
N = 112 1 RCT[86]	RR, 0.84; 95% CI, 0.59 to 1.20	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Voice Alteration or Hoarseness			
N = 112 1 RCT[86]	RR, 18.24; 95% CI, 0.44 to 750.38	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Cough			
N = 112 1 RCT[86]	Not reported		
Outcome: Dyspnea			
N = 112 1 RCT[86]	Not reported		

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

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

Table 9. GRADE Summary of Evidence: Effectiveness of tVNS in Epilepsy

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

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

Table 10. GRADE Summary of Evidence: Harms of tVNS in Epilepsy

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
High-stimulation tVNS vs. Low-stimulation tVNS			
Outcome: Treatment Withdrawals			
N = 76 1 RCT[79]	RR, 1.32; 95% CI, 0.58 to 2.97	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Voice Alteration or Hoarseness			
N = 76 1 RCT[79]	None were observed	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Cough			
N = 76 1 RCT[79]	None were observed	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Dyspnea			
N = 76 1 RCT[79]	Not reported		
Outcome: Pain			
N = 76 1 RCT[79]	RR, 2.11; 95% CI, 0.38 to 11.81	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Paresthesias			
N = 76 1 RCT[79]	Not reported		
Outcome: Nausea			
N = 76 1 RCT[79]	RR, 1.05; 95% CI 0.14 to 7.93	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Headache			
N = 76 1 RCT[79]	RR, 0.90; 95% CI 0.40 to 2.06	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)

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

Table 11. GRADE Summary of Evidence: Cost-effectiveness of VNS for Epilepsy

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

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

Depression

We found 5 studies, reported in 9 publications, which evaluated the benefits and harms of VNS for depression (Table 12 and Appendix C, Tables C1 to C3, C10 to C15, and C27 to C31).[56,59,61,62,70,74,78,84,85] We rated the risk of bias in these studies as follows:

- 2 RCTs had a moderate risk of bias due to concerns about randomization, author conflicts of interest, and industry funding.
- 1 NRS had a moderate risk of bias due to concerns about industry funding and author conflict of interest.
- 2 NRS had a high risk of bias due to serious concern about patient selection, the lack of adjustment for confounding, and industry funding.

We did not assess any of the studies as having a low risk of bias.

Table 12. Characteristics of Eligible Studies Evaluating VNS for Depression

Study Study Risk of Bias	NCT Number and Study Name Setting	Population	FDA-approved Indication	VNS	Comparator
RCTs					
Aaronson et al., 2013[78] Moderate	NCT00305565, D-21 29 academic and clinical sites in the U.S.	Adults with TRD	Yes	High-stimulation VNS Medium-stimulation VNS	Low-stimulation VNS
Rush et al., 2005[85]	NCT00533832 21 sites in the U.S.	Adults with TRD	Yes	VNS	Sham VNS (device was not turned on)

Study Study Risk of Bias	NCT Number and Study Name Setting	Population	FDA-approved Indication	VNS	Comparator
Nierenberg et al., 2008[84] Moderate					
Nonrandomized Studies and Registry-based Studies					
Aaronson et al., 2017[56] Conway et al., 2018 [59] Kumar et al., 2019[70] Moderate	NCT00320372 61 U.S. sites	Adults with TRD	Yes	VNS, plus treatment as usual	Treatment as usual
Feldman et al., 2013[61] High	Not reported Medicare claims database, U.S.	Adults with TRD	Yes	VNS	Treatment as usual
George et al., 2005[62] Rush et al., 2005[74] High	Not reported 22 U.S. sites	Adults with TRD	Yes	VNS, plus treatment as usual	Treatment as usual

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

We also found 1 RCT that evaluated the benefits and harms of tVNS for depression (Table 13 and Appendix C, Tables C1 and C3).[81] We rated the risk of bias of this study as high because of concerns about the lack of reporting about methods, the small sample size, and conflicts of interest not being reported.

Table 13. Characteristics of Eligible Studies Evaluating tVNS for Depression

Study ID Study Risk of Bias	NCT Number and Study Name Setting	Population	FDA-approved Indication	tVNS	Comparator
RCTs					
Hein et al., 2013[81] High	Not reported Psychiatric hospital, Germany	Adults with MDE	No	tVNS (once or twice a day)	Sham tVNS (device was turned off)

Abbreviations. MDE: major depressive episode; NCT: U.S. National Clinical Trial; RCT: randomized controlled trial; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

Study Characteristics

All of the studies evaluated the use of VNS in adults with TRD in multiple sites across the U.S.[56,61,62,78,85] In the 2 RCTs, the effect of 3 different stimulation VNS protocols was evaluated in 1 RCT (Table 14)[78] with the other RCT comparing VNS with sham VNS.[85] In the 3 NRSs, VNS was compared with TAU.[56,61,62] The study by George et al., reported in 2 publications,[62,74] compared the long-term follow-up of participants with VNS in the RCT by Rush et al.[85] with another naturalistic, observational study of participants receiving TAU.

Table 14. VNS Parameters in Studies Comparing High- vs. Low-stimulation VNS for Depression

VNS Stimulation Parameter	Aaronson et al., 2013[78]		
	High	Medium	Low
Current (mA)	1.25	0.5 to 1.0	0.25
Frequency (Hz)	20	20	20
Pulse Width (µsec)	250	250	130
On Time	30 seconds	30 seconds	30 seconds
Off Time	5 minutes	5 minutes	5 minutes
Manual Activation Mode	NR	NR	NR

Abbreviations. µsec: microsecond; Hz: Hertz; mA: milliamp; NR: not reported; VNS: vagal nerve stimulation.

Hein et al.[81] compared tVNS with sham tVNS in adults with major depressive disorder. The study was conducted in a single psychiatric hospital in Germany.[81]

Study Findings

Depression Severity

We identified 2 eligible RCTs[78,85] and 1 eligible NRS[62] reporting measures of depression severity. Patients in the high- and low-stimulation groups experienced a numerical reduction in depression severity at week 22, but there was no significant difference between the groups ($P > .80$).[78] Improvements continued to week 50, but again, there were no significant differences between the high- and low-stimulation groups ($P > .05$).[78] Similar results were seen for the medium-stimulation group compared with high- and low-stimulation VNS.[78]

In the RCT by Rush et al.,[85] participants in the VNS and sham VNS group experienced improvements in depression severity, assessed using a range of measures. However, the differences between groups were not statistically different.[85]

In the NRS, participants in the VNS plus TAU group had a greater reduction in depression symptoms than participants in the TAU group (mean difference in total Inventory of Depressive Symptomatology Self Report score per month, -0.40: $P < .001$)[62] However, it is not clear if this difference was clinically meaningful.

Mortality

We identified 2 eligible RCTs[78,85] and 2 eligible NRSs[56,61] reporting mortality.

High-stimulation VNS was not associated with lower rates of suicide death or attempts compared with low-stimulation VNS (Figure 25 and Figure 26). The investigators considered the suicides to be not related to VNS implantation or stimulation (1 patient in the low-stimulation group had a history of 2 lifetime suicide attempts and 1 patient in the high-stimulation group had

no history of prior suicide attempts). No patients died by suicide in the medium-stimulation group and the rates of attempted suicide were similar between the medium- and low-stimulation groups.[78] Another 4 patients died during the study period: 1 patient died from a pulmonary embolism following bariatric surgery; 1 patient died in a motor vehicle accident; and 2 patients with pre-existing cardiovascular disease died from cardiovascular system related causes.[78]

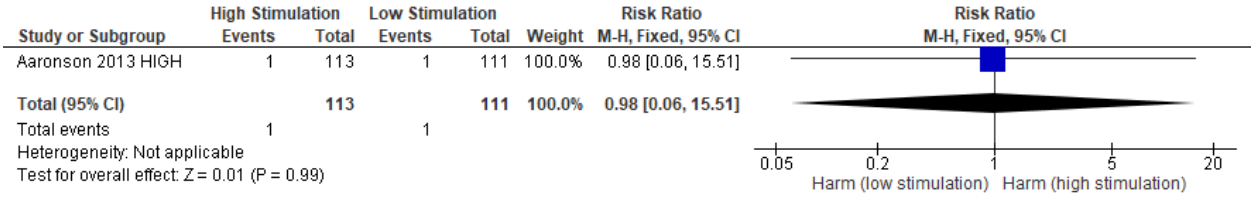

Figure 25. High- vs. Low-stimulation, Outcome: Suicide Death

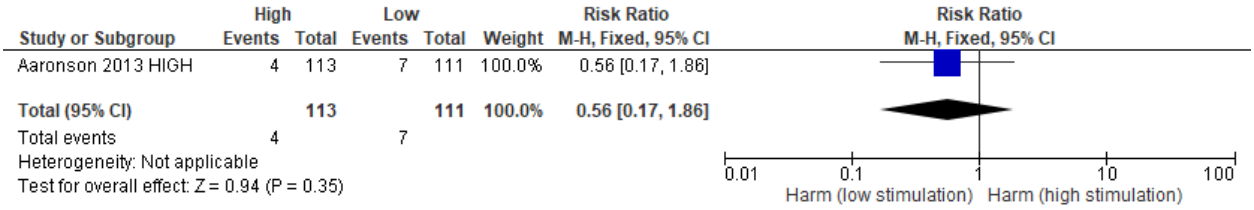

Figure 26. High- vs. Low-stimulation, Outcome: Suicide Attempt

Rush et al.[85] reported no difference in the rate of suicide between VNS and sham VNS (

Figure 27). In the VNS group, 1 participant died by suicide after 5 weeks of treatment, which was assessed as being condition-related and not treatment-related.[85]

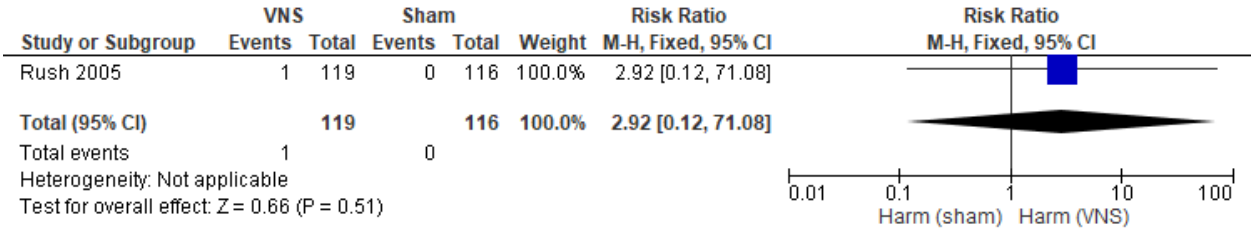

Figure 27. VNS vs. Sham, Outcome: Suicide Death

Analysis of the VNS Patient Outcome Registry showed that the number of deaths due to any cause in the VNS and TAU groups were similar (all-cause mortality per 1,000 person-years: VNS+TAU, 3.53; 95% CI, 1.41 to 7.27; vs. TAU, 8.63; 95% CI, 3.72 to 17.01; *P* value not reported). [56] Also, participants in both groups had similar rates of suicide death (suicides per 1,000 person-years: VNS+TAU, 1.01; 95% CI, 0.11 to 3.64; vs. TAU, 2.20; 95% CI, 0.24 to 7.79; *P* value not reported).[56] Although formal statistical testing was not reported for either outcome, the 95% CIs between groups overlapped for each outcome, indicating that they were likely not significantly different.

In the VNS Medicare population, 37 patients (5%) died during the 2-year post-implantation study period; however, this rate was much lower than patients with TRD or managed depression (overall mortality rate per 1,000 patient years: VNS, 19.9; TRD, 46.2; managed depression, 46.8; $P < .001$).[61] Rates of suicide attempt or self-inflicted injury appeared higher in the VNS population during the study period (VNS: 10% in year 1, 15% in year 2; TRD: 7% over 2 years; managed depression: 1% over 2 years).[61] However, it is not clear if this difference is statistically, significant as no formal statistical analysis was conducted, nor is it clear if this is associated with VNS use or whether it reflects greater severity of depression in the VNS group.

Suicidal Ideation and Severity

Of the 5 eligible studies, 2 NRSs reported measures of suicidal ideation and severity.[56,61]

Participants in the VNS group experienced greater reductions of suicidality on 2 specific items, 1 patient-reported and 1 clinician-assessed (odds ratio [OR] of a score of 2 or 3 on QIDS-SR item 12: 2.11; 95% CI, 1.28 to 3.48; OR for the investigator-completed suicidality assessment: 2.0; 95% CI, 1.08 to 3.86), but not for suicidal thoughts (MADRS item 10: OR 1.67; 95% CI, 0.98 to 2.83).[56]

In the study by Feldman et al.,[61] suicidal ideation appeared higher in the VNS group (VNS: 8% in year 1, 14% in year 2; TRD: 6% over 2 years; managed depression: 1% over 2 years).[61]

Response and Duration of Response

We identified 2 eligible RCTs[78,85] and 1 eligible NRS[62] reporting on response rates and duration of response.

High-stimulation VNS was associated with greater rates of response, defined as a reduction of 50% or more in Montgomery-Åsberg Depression Rating Scale (MADRS) score, compared with low-stimulation VNS (Figure 28). However, the summary estimate was sensitive to missing data, with a worse-case analysis showing that high-stimulation VNS was associated with similar responses rates compared with low-stimulation VNS (RR, 1.40; 95% CI, 0.86 to 2.30; Appendix F). Response rates were also not significantly different between the medium-stimulation and low-stimulation groups.[78] Participants in the high- and medium-stimulations groups experienced greater rates of sustained response (the number of responders at week 22 who continued to response at week 50) as measured by the Inventory of Depressive Symptomatology – Clinician version (IDS-C; high-stimulation, 81.8%; medium-stimulation, 88.2%; low-stimulation, 43.8%; low vs. medium, $P = .02$; low vs. high, $P = .02$) but not the MADRS (high-stimulation, 76.7%; medium-stimulation, 92.0%; low-stimulation, 68.8%; $P > .05$).[78]

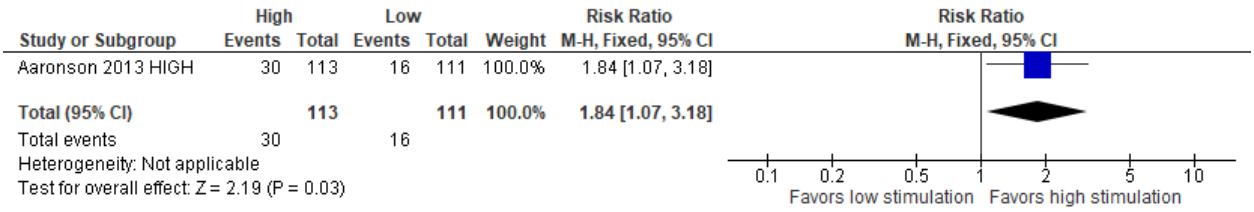

Figure 28. VNS High- vs. Low-stimulation, Outcome: 50% or More MADRS Response

When compared with sham VNS, 50% MADRS response rates were similar for active VNS (Figure 29), and results remained nonsignificant in the best- and worst-case analyses (Appendix F).

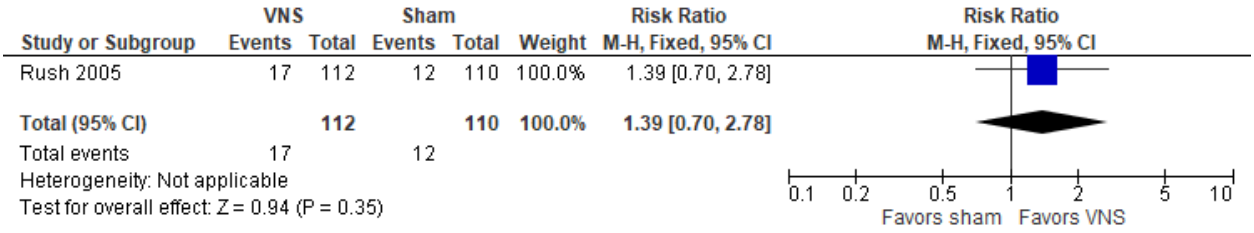

Figure 29. VNS vs. Sham, outcome: 50% or More MADRS Response

Participants in the VNS+TAU group experienced greater response rates at 5 years, compared with TAU on a range of measures (67.6% vs. 40.9%; *P* < .001) and had a shorter time to first response (median time to first response, based on MADRS score: VNS+TAU, 12 months; TAU, 48 months; *P* < .001), and a longer time to recurrence (median time to recurrence, based on MADRS score: VNS+TAU, 12 months; TAU, 7 months; *P* < .001).[56] Time to first response was also shorter, based on the Quick Inventory of Depressive Symptoms - Self-Report version (QIDS-SR) but the time to recurrence was not statistically significant.[56]

In the study by George et al.,[62] participants in the VNS+TAU group continued to experience reductions in symptoms of depression over time, compared with TAU. Participants in the VNS+TAU group had higher rates of response as measured by the Hamilton Rating Scale for Depression (HRSD; 26.8% vs. 12.5%; *P* = .01), but not when using the Inventory of Depressive Symptomatology – Self Report version (IDS-SR; 19.6% vs. 12.1%; *P* = .11).[62] More patients in the VNS+TAU group experienced a sustained response at 12 months (55.2% vs. 14.3%; *P* value not reported) and more patients in the VNS+TAU group who did not respond at 3 months had a response at 12 months (14.4% vs. 11.5%; *P* value not reported).[62]

Remission and Duration of Remission

We identified 1 eligible RCT[78] and 2 eligible NRSs[56,62] reporting remission and duration of remission.

At week 22 and at week 50, individuals in the high-, medium-, and low-stimulation groups had similar rates or remission, defined as score of ≤ 14 on the IDS-C and IDS-SR, ≤ 5 on the Quick Inventory of Depressive Symptomatology – Clinician version (QIDS-C), or ≤ 9 on the MADRS (results reported graphically).[78]

In the NRS by Aaronson et al.,[56] patients in the VNS+TAU group had higher remission rates at 5 years, defined as a MADRS score of < 9 (43.3% vs. 25.7%; *P* < .001), as a QIDS-SR score of ≤ 5 (40.4% vs. 25.0%; *P* < .001), and as Clinician Global Impression – Improvement (CGI-I) score of 1 (49.7% vs. 21.4%; *P* < .001).[56] Participants in the VNS+TAU group also had a shorter time to remission (median time to remission, based on the MADRS score: VNS+TAU, 49 months; TAU, 65 months; *P* < .001), but not a longer duration of remission (median duration, based on the

MADRS score: VNS+TAU, 40 months; TAU, 19 months; *P* = .10; median duration, based on the QIDS-SR score: VNS+TAU, 30 months; TAU, 18 months; *P* = .20).[56]

George et al.[62] reported that participants in the VNS+TAU group had higher rates of response, as measured by IDS-SR (13.2% vs. 3.2%; *P* = .007).[62]

Anxiety

We identified 1 eligible RCT[78] and 1 eligible NRS[61] reporting on rates of anxiety.

In the RCT, patients experienced similar levels of anxiety rates (high-stimulation, 11.5%; medium-stimulation, 11.2%; low-stimulation, 11.7%; *P* value not reported).[78]

In the VNS Medicare population, patients appeared to experience lower rates of anxiety, obsessive compulsive disorders, or phobias (VNS: 11% in year 1, 16% in year 2; TRD: 59% over 2 years; managed depression: 43% over 2 years; *P* value not reported).[61]

Treatment Withdrawal

We identified 2 eligible RCTs[78,85] and 1 NRS reporting withdrawals. Both RCTs reported similar levels of withdrawals between high-, medium-, and low-stimulation VNS[78] (Figure 30, high-stimulation vs. low-stimulation) and between VNS and sham VNS (Figure 31).[85]

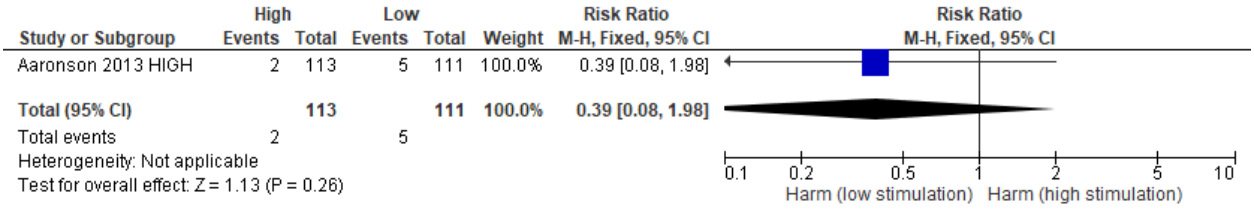

Figure 30. High- vs. Low-stimulation, Outcome: Withdrawals

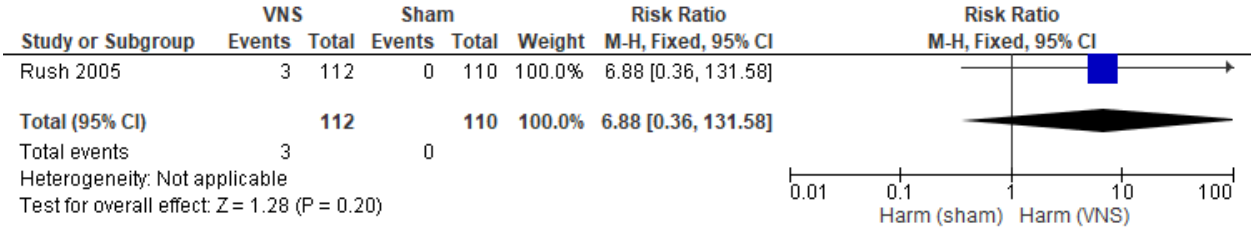

Figure 31. VNS vs. Sham, Outcome: Withdrawals

In the NRS, completion rates were higher in the VNS+TAU group than in the TAU group (93% vs. 74% at 1 year; 59% vs. 62% at 2 years, 63% vs. 56% at 3 years; 68% vs. 50% at 4 years, 61% vs. 46% at 5 years), but formal statistical testing was not conducted.[56]

Compliance with Other Depression Treatment

We did not identify any eligible studies reporting compliance with other depression treatment.

Cognitive Changes

We did not identify any eligible studies reporting cognitive changes, other than depression or anxiety.

Quality of Life

We identified 1 eligible RCT[85] and 1 NRS[56,59] reporting quality of life outcomes.

In the RCT, participants in the VNS and sham VNS groups reported similar changes in the physical (mean change in the physical component: VNS, -0.9; sham, -1.6; *P* = .48) and mental components of the Short Form Health Survey-36 (mean change in the mental component: VNS, 5.0; sham, 4.0; *P* = .41).[85]

In the NRS, participants in the VNS+TAU group at 3 months improved significantly compared with TAU (reported graphically; *P* value not reported) and was sustained over the 5 years of the study.[56,59] The change in quality of life corresponded to a change in MADRS score of 34% (lower than the usual minimal important difference of 50% change from baseline). [56,59]

Sleep

We did not identify any eligible studies reporting sleep outcomes.

Harms

We identified 5 eligible studies, 2 RCTs[78,85] and 3 NRSs[56,61,62], reporting the direct harms of VNS for depression.

Patients in the high-stimulations VNS group did not experience higher rates of VNS-related adverse events than patients in the low-stimulation VNS group (Figures 32 to 38).

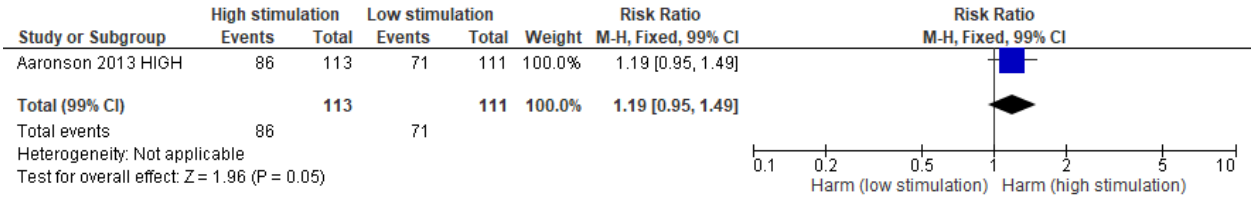

Figure 32. High- vs. Low-stimulation, Outcome: Voice Alteration or Hoarseness

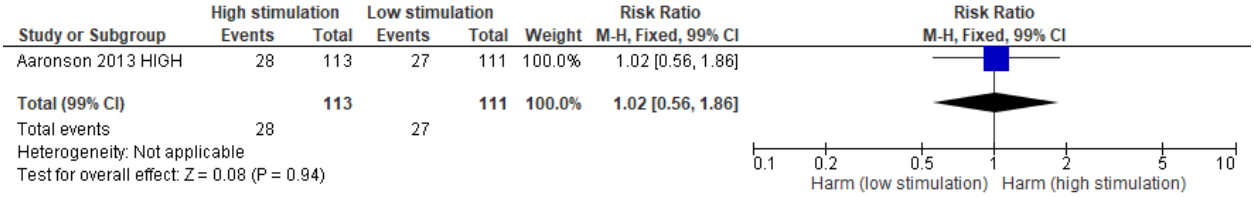

Figure 33. High- vs. Low-stimulation, Outcome: Cough

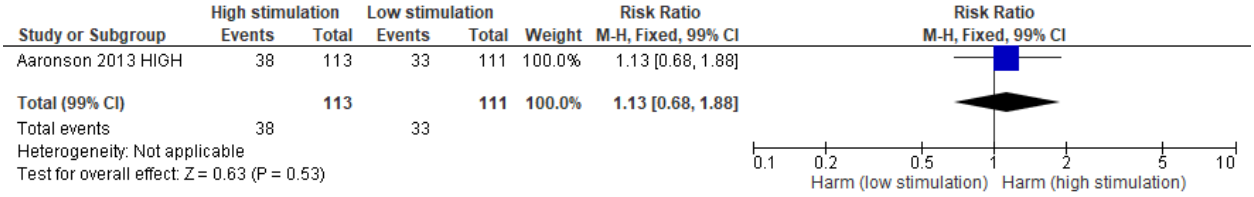

Figure 34. High- vs. Low-stimulation, Outcome: Dyspnea

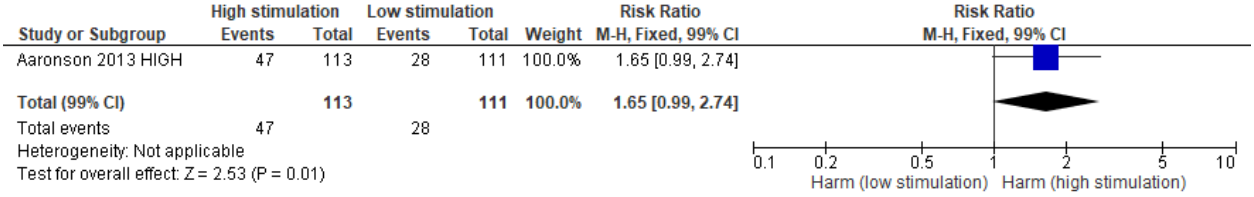

Figure 35. High- vs. Low-stimulation, Outcome: Pain

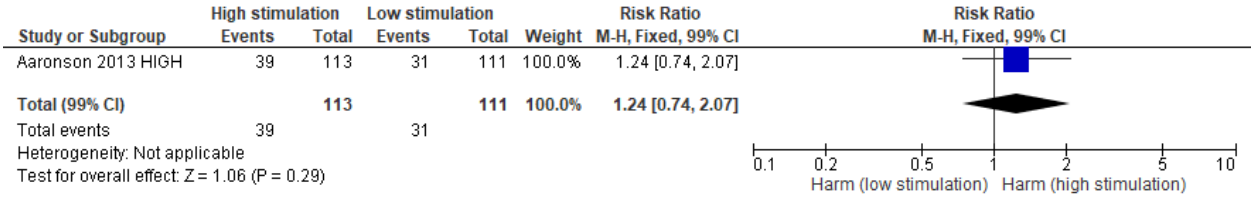

Figure 36. High- vs. Low-stimulation, Outcome: Paresthesias

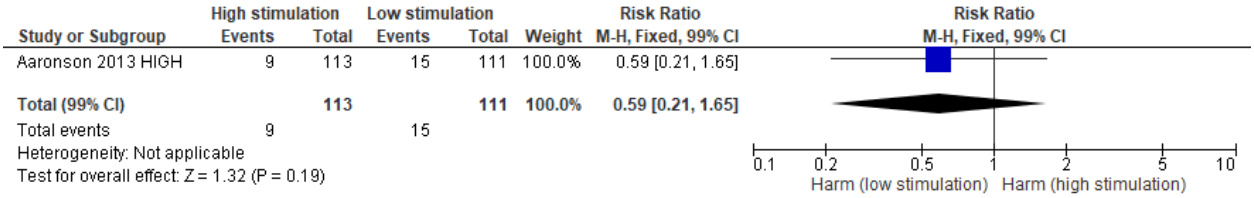

Figure 37. High- vs. Low-stimulation, Outcome: Nausea

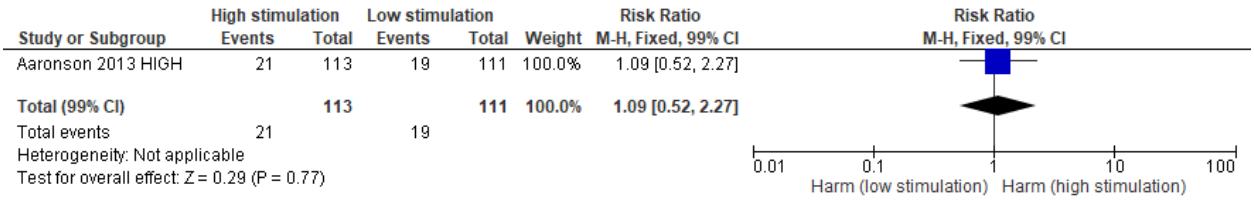

Figure 38. High- vs. Low-stimulation, Outcome: Headache

Patients in the VNS group experienced higher rates of voice alteration or hoarseness and cough than patients in the sham group, but both groups experienced similar rates of dyspnea, pain, paresthesias, and nausea (Figures 39 to 44). Rates of headaches were not reported.[85]

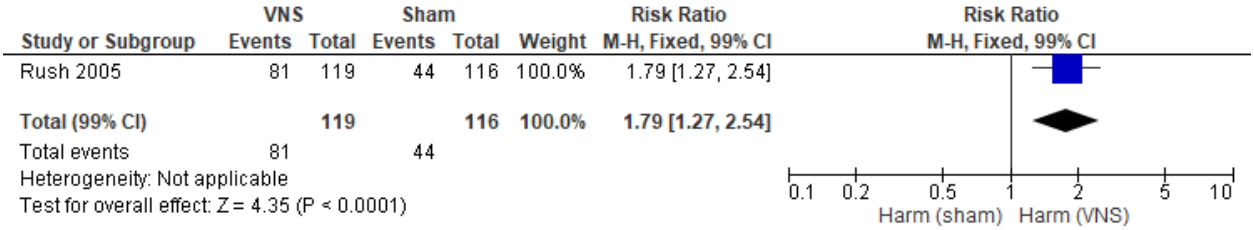

Figure 39. VNS vs. Sham VNS, Outcome: Voice Alteration or Hoarseness

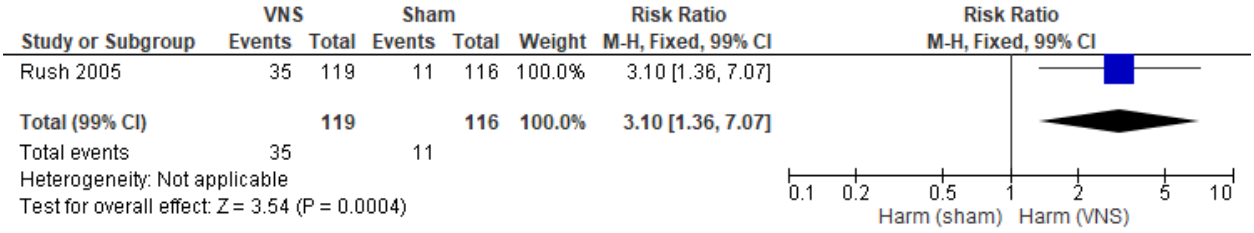

Figure 40. VNS vs. Sham VNS, Outcome: Cough

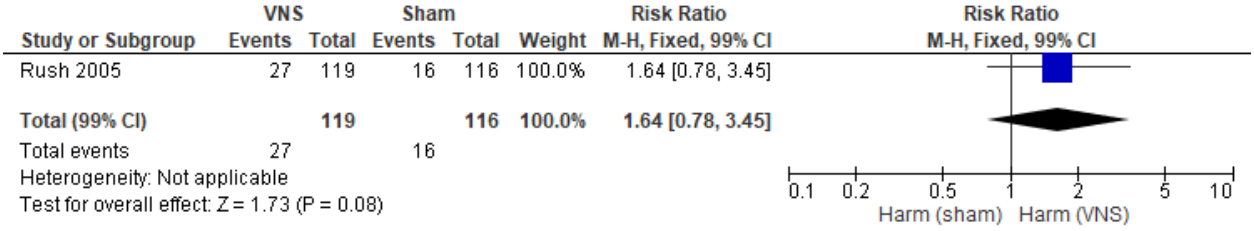

Figure 41. VNS vs. Sham VNS, Outcome: Dyspnea

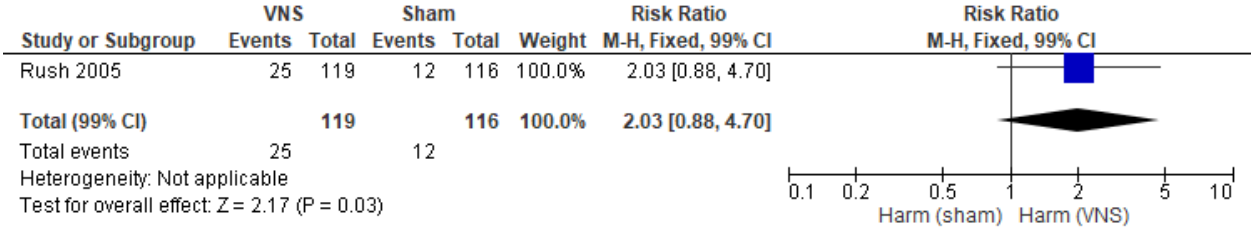

Figure 42. VNS vs. Sham VNS, Outcome: Pain

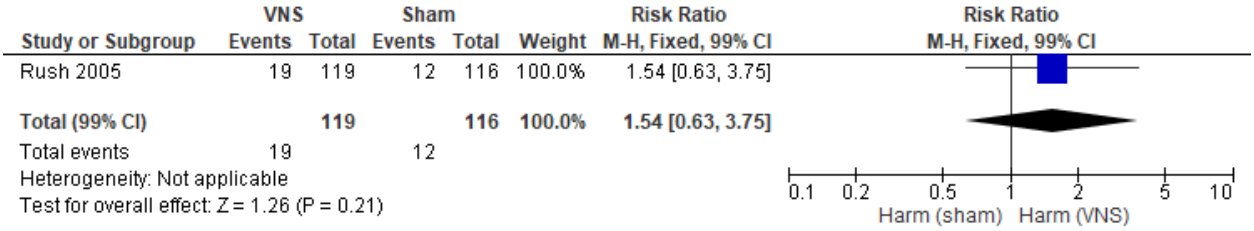

Figure 43. VNS vs. Sham VNS, Outcome: Paresthesias

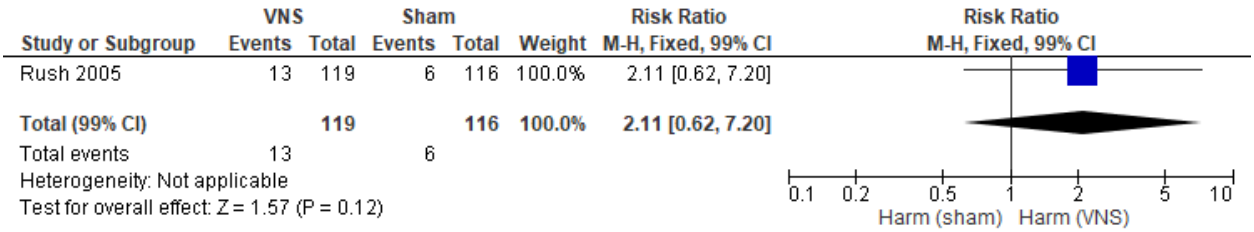

Figure 44. VNS vs. Sham VNS, Outcome: Nausea

In the NRS by Feldman et al.[61]:

- In the VNS group, 150 of 629 (24%) experienced no negative events (defined as no emergency room use, no psychiatric hospitalizations, no hospitalization for poisoning, no ECT, no diagnoses for poisoning, self-injury, self-harm, or suicidal ideation).
- In the VNS group, 197 of 629 (31%) experienced a negative event (defined as any amount of ECT postimplantation, two or more psychiatric hospitalizations (could include psychiatric as well as hospitalization for a poisoning or other self-harm/suicidal ideation diagnosis, or 2 or more diagnoses on claims of poisoning, suicidal ideation, self-harm, or self-injury).
- In the first and second year post-identification period, 1,429 of 3,797 (38%) in the TRD group had no negative events and 767 (20%) had negative events.
- In the first and second year post-identification period, 2,979 of 6,005 (50%) in the managed depression group had no negative events and 219 (4%) had negative events.

Formal statistical testing was not conducted. [61]

Reimplantation

We did not identify any eligible studies reporting the rates of reimplantation.

Failure Rate

We did not identify any eligible studies reporting failure rates.

Transcutaneous VNS

We identified 1 eligible RCT comparing tVNS and sham tVNS.[81] Participants in the active and sham tVNS groups had similar changes in the Hamilton Depressing Rating Scale (HAM-D) from baseline (-5.4 vs. -6.6; *P* > .05) and the Beck Depression Inventory (BDI; -12.6 vs. -4.4; *P* > .05).[81] No other measures of effectiveness were reported.[81] The RCT by Hein et al.[81] did not report harms by treatment group but noted that no unpleasant sensations were reported during or after the stimulation procedures, no local skin irritations or unpleasant acoustic or vestibular reactions were observed, and no adverse side effects were observed or reported after the trial ended.

GRADE Summary of Findings

Table 15. GRADE Summary of Evidence: Effectiveness of VNS for Depression

Number of Participants (N) Studies	Findings	Certainty of Evidence	Rationale
High-stimulation VNS vs. Low-stimulation VNS			
Outcome: Depression Severity, Measured on the IDS-C			
N = 224 1 RCT[78]	No difference between 3 VNS stimulation protocols	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)
Outcome: Suicide			
N = 224 1 RCT[78]	RR, 0.98; 95% CI, 0.06 to 15.51	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Attempted Suicide			
N = 224 1 RCT[78]	RR, 0.56; 95% CI, 0.17 to 1.86	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Response, Defined as 50% Reduction or More, Measured on the MADRS			
N = 224 1 RCT[78]	RR, 1.84; 95% CI, 1.07 to 3.18	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
VNS vs. Sham VNS			
Outcome: Depression Severity, Measured on the HRSD			
N = 222 1 RCT[85]	Estimated difference -0.77; 95% CI, -2.34 to 0.80	⨁⨁⨁◯ MODERATE	Downgraded 1 level for risk of bias
Outcome: Depression Severity, Measured on the IDS-SR			
N = 222 1 RCT[85]	Estimated difference -2.37; 95% CI, -4.78 to 0.03	⨁⨁⨁◯ MODERATE	Downgraded 1 level for risk of bias
Outcome: Suicide			
N = 235 1 RCT[85]	RR, 2.92; 95% CI, 0.12 to 71.08	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Response, Defined as 50% Reduction or More, Measured on the MADRS			
N = 222 1 RCT[85]	RR, 1.39; 95% CI, 0.70 to 2.78	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
VNS+TAU vs. TAU			
Outcome: Mean Difference in Reduction of Depressive Symptoms, Measured on the IDS-SR			
N = 329 1 NRS[62]	VNS+TAU was associated with a greater reduction in depressive symptoms than TAU alone; however, the difference may not be clinically meaningful	⨁◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)

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

Note. Nonrandomized studies start at LOW in the GRADE framework. Abbreviations. CI: confidence interval; HRSD: Hamilton Rating Scale for Depression; IDS-C: Inventory of Depressive Symptomatology - Clinician version; IDS-SR: Inventory of Depressive Symptomatology - Self Report version; MADRS: Montgomery-Åsberg Depression Rating Scale; NRS: nonrandomized study; RCT: randomized controlled trial; RR: risk ratio; TAU: treatment as usual; VNS: vagal nerve stimulation.

Table 16. GRADE Summary of Evidence: Harms of VNS in Depression

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
High-stimulation VNS vs. Low-stimulation VNS			
Outcome: Treatment Withdrawals			
N = 224 1 RCT[78]	RR, 0.39; 95% CI, 0.08 to 1.98	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Voice Alteration or Hoarseness			
N = 224 1 RCT[78]	RR, 1.19; 95% CI, 0.95 to 1.49	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Cough			
N = 224 1 RCT[78]	RR, 1.02; 95% CI, 0.56 to 1.86	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Dyspnea			
N = 224 1 RCT[78]	RR, 1.13; 95% CI, 0.68 to 1.88	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Pain			
N = 224 1 RCT[78]	RR, 1.65; 95% CI, 0.99 to 2.74	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Paresthesias			
N = 224 1 RCT[78]	RR, 1.24; 95% CI, 0.74 to 2.07	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Nausea			
N = 224 1 RCT[78]	RR, 0.59; 95% CI, 0.21 to 1.65	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Headache			
N = 224 1 RCT[78]	RR, 1.09; 95% CI, 0.52 to 2.27	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)

Number of Participants (N) Number of Studies	Findings	Certainty of Evidence	Rationale
VNS vs. Sham VNS			
Outcome: Treatment Withdrawals			
N = 222 1 RCT[85]	RR, 6.88; 95% CI, 0.36 to 131.58	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Voice Alteration or Hoarseness			
N = 235 1 RCT[85]	RR, 1.79; 95% CI, 1.27 to 2.54	⨁⨁⨁◯ MODERATE	Downgraded 1 level for risk of bias
Outcome: Cough			
N = 235 1 RCT[85]	RR, 3.10; 95% CI, 1.36 to 7.07	⨁⨁⨁◯ MODERATE	Downgraded 1 level for risk of bias
Outcome: Dyspnea			
N = 235 1 RCT[85]	RR, 1.64; 95% CI, 0.78 to 3.45	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Pain			
N = 235 1 RCT[85]	RR, 2.03; 95% CI, 0.88 to 4.70	⨁⨁◯◯ LOW	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)
Outcome: Paresthesias			
N = 235 1 RCT[85]	RR, 1.54; 95% CI, 0.63 to 3.75	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Nausea			
N = 235 1 RCT[85]	RR, 2.11; 95% CI, 0.62 to 7.20	⨁◯◯◯ VERY LOW	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)
Outcome: Headache			
N = 235 1 RCT[85]	Not reported		
VNS vs. TAU			
Outcome: Treatment Withdrawals			
N = 222 1 NRS[56]	Completion rates were higher in the VNS+TAU group than in the TAU group, but formal statistical testing was not conducted	⨁◯◯◯ VERY LOW	Downgraded 1 level each for risk of bias and for imprecision (i.e., wide CIs)

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

Table 17. GRADE Summary of Evidence: Effectiveness of tVNS in Depression

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

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

Table 18. GRADE Summary of Evidence: Harms of tVNS in Depression

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

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

FDA Reported Harms for Epilepsy and Depression

We also searched the U.S. FDA MAUDE database for the last 5 years and the Medical Device Recall reports (Appendix G, Tables G1 and G2). We found 397 entries in the MAUDE database, including voluntary, user facility, distributor, and manufacturer reports of adverse events relating to VNS use in the last 5 years. We were not able to analyze the reports by condition, but the types of adverse events appeared similar to those reported in our eligible studies for epilepsy and depression.

Recalls documented in the Medical Device Recall database included errors in impedance measurements, unintended warning messages, miscalculations resulting in inappropriate VNS stimulation (both higher and lower levels of stimulation than expected), reductions in device and battery longevity, and lead fractures (Appendix G).

In December 2019, the FDA issued a Class I recall, the most serious type of recall, where problems with the recalled devices may cause serious injuries or death.[90] The FDA reported that LivaNova is recalling the VNS Therapy SenTiva Generator System due to an unintended reset

error that causes the system to stop delivering VNS therapy.[90] If device replacement is needed, there is a risk associated with additional surgery to replace the generator.[90] At the time of recall, LivaNova had received 14 reports of unexpected reset errors, and 4 patients who required early revision surgery for failed devices.[90] No deaths related to this issue were reported.[90] On July 31, 2019, LivaNova implemented additional mitigations and at the time of recall, no reset errors had been observed since the implementation of these mitigations.[90] The additional mitigations remain review by the FDA.[90]

Patients were advised to notify a health care provider immediately if there was a change in symptoms, such as increase in seizures or depressive symptoms, or perceived loss of stimulation.[90] Caregivers of children implanted with an affected device were advised to have the health care provider verify that the device is functioning properly.[90] Patients and their health care provider were also encouraged to:[90]

- Use the magnet regularly, if magnet mode was used for epilepsy, to verify that stimulation is felt as described in the labeling.
- Ensure that the device is programmed to the intended settings, such as programming at last visit, and per scheduled programming protocol at the beginning of each office visit.
- Ensure that the device is programmed to the intended settings at the end of each office visit.
- Complete the Customer Response Form attached to the notification and have the health care provider submit it to the company.

Health care providers were also advised to:[90]

- Verify settings during titration visits for initial and replacement implants to ensure the VNS device is not affected by the issue for device disablements device disablements within the first 60 days of use.
- Consider seeing patients with scheduled programming protocols enabled on their device more frequently during the first 60 days of titration.
- Continue to follow LivaNova's general recommendations in labeling to monitor the patient regularly for patients whose therapy has been enabled for greater than 60 days.
- Contact the manufacturer immediately if the generator is found to be unexpectedly disabled, and provide patients with information on alternate therapy.

Key Question 3

Epilepsy

We identified a further 2 NRSs evaluating the benefits and harms of VNS by patient characteristic.[57,65] We assessed each of these studies for risk of bias. We rated the risk of bias of the study by Amar et al.[57] as high because of serious concerns around patient selection, no accounting for confounding, and conflicts of interest. We rated the risk of bias of the study by Helmers et al.[65] as high, because of concerns around the lack of adjustment for confounding and for industry funding.[65,119]

Prior Cranial Surgery

Amar et al.[57] aimed to determine the effectiveness of VNS in patients with persistent or recurrent seizures after surgery for intractable epilepsy, compared with patients who had not had surgery.[57] Patients who had prior cranial surgery had lower rates of response, defined as a

50% reduction or more in seizure frequency at 12 months (response: prior surgery, 45.7%; no prior surgery, 60.0%; $P < .001$), but the rates were similar at 24 months (response: prior surgery, 55.1%; no prior surgery, 62.2%; $P > .05$).[57] Both groups reported similar levels of seizure freedom at 12 and 24 months.[57] At 12 months, patients who had no prior cranial surgery also experienced more improved mood ($P < .001$), improved memory ($P = .02$), and improved verbal communication ($P = .01$) than patients in the prior surgery group, but these differences were not statistically different at 24 months.[57] Similarly, at 12 months, prior surgery was associated with a lower quality of life but at 24 months, most measures of quality of life were similar between the surgery and no surgery groups.[57]

Early or Late Treatment with VNS

Helmers et al.[65] compared changes in seizure frequency in 2 groups of patients with pharmacoresistent seizures: the early treatment group, who began VNS therapy 6 years or less after the onset of seizures, and the late treatment group, who began VNS therapy more than 6 years after the onset of seizures. At 12 months, patients in the early and late treatment groups had similar reductions in seizure frequency (50% vs. 57%; $P > .05$), and response rates, defined as a reduction in 50% or more, 75% or more, and 90% or more, were similar between the two groups at 3 and 12 months.[65] However, patients treated in the early treatment group were more likely to become seizure-free at 12 months (11.8% vs. 4.5%; $P = .03$).[65]

Depression

Prior ECT

The study by Aaronson et al.[56] showed that VNS+TAU resulted in better rates of response at 5 years overall. Aaronson et al.[56] compared outcomes for patients who had completed 1 or more adequate courses of ECT, by response to ECT treatment. Patients in the VNS+TAU group who had previously responded to ECT had higher response rates than patients in the TAU group (71.3% vs. 56.9%; $P = .006$). Patients in the VNS+TAU group who had not previously responded to ECT also had higher response rates than patients in the TAU group (59.6% vs. 34.1%; $P < .001$).[56]

Comorbid Anxiety

Individuals with comorbid anxiety had similar rates of response to VNS to those without comorbid anxiety (results reported graphically).[56]

Type of Depression (bipolar vs. unipolar)

Nierenberg et al.[84] compared the outcome of VNS for bipolar and unipolar TRD patients participating in the 2005 randomized, sham-controlled trial of VNS.[85] Patients with bipolar and unipolar depression had similar results over 12 months for response and quality of life.[84]

In a NRS, patients with bipolar depression had similar rates of response to VNS to those patients with unipolar depression (results reported graphically).[56] Another NRS also found similar results between bipolar and unipolar depression[62]:

- At 12 months, the overall IDS-SR response rate was 22% for the VNS+TAU group, with a response rate of 21% for people with MDD, and 29% for people with bipolar disorder (*P* values not reported).

- At 12 months, the overall Hamilton Rating Scale for Depression (HRSD) response rate was 30% for the VNS+TAU group, with a response rate of 30% for people with MDD, and 29% for people with bipolar disorder (*P* values not reported).
- At 12 months, the overall IDS-SR response rate was 12% for the TAU group, with a response rate of 12% for people with MDD, and 7% for people with bipolar disorder (*P* values not reported).
- At 12 months, the overall HRSD response rate was 13% for the TAU group, with a response rate of 12% for people with MDD, and 15% for people with bipolar disorder (*P* values not reported).

Age

In the study comparing VNS with TAU in the Medicare population, mortality rates were significantly lower in the VNS group than the TRD and managed depression groups for all age bands, other than for people under 40 years of age.[61]

Key Question 4

Epilepsy

We identified 2 eligible studies reporting economic outcomes for VNS in epilepsy (Table 19, and Appendix C, Tables C32 to C42).[88,89] We did not identify any eligible studies reporting the economic outcomes of tVNS for epilepsy. We assessed both included studies as having moderate risk of bias, because of concerns about author conflicts of interest and the modeling approach.

Table 19. Study Characteristics of Eligible Economic Studies Evaluating VNS for Epilepsy

Study ID Study Risk of Bias	Population	Intervention	Comparators	Economic Analytic Method
Fallah et al., 2016[88] Moderate	Theoretical cohort of children with focal drug-resistant epilepsy secondary to Tuberous Sclerosis Complex that is amenable to surgery	VNS	• Resective surgery • Ketogenic diet • mTOR inhibitor • Addition of another AED	Cost-utility analysis
Purser et al., 2018[89] Moderate	Theoretical cohort of patients aged 12 or older with drug-resistant partial-onset seizures	VNS	• No VNS	Budget impact model

Abbreviations. AED; antiepileptic drug; mTOR: mammalian target of rapamycin; VNS: vagal nerve stimulation.

Study Findings

Fallah et al. conducted a cost-utility analysis from a third-party payer perspective, for children with drug-resistant tuberous sclerosis complex that had failed to improve with 2 AEDs and that was amenable to resective epilepsy surgery.[88] The time-horizon was 5 years.[88] The analysis compared 4 strategies:

- Resective epilepsy surgery
- VNS

- Ketogenic diet
- Addition of a third AED (specifically, carbamazepine)

Given a willingness-to-pay of $100,000 per quality-adjusted life year (QALY), the addition of a third AED was the most cost-effective treatment strategy.[88] This strategy resulted in an estimated cost of $6,568.49 for a gain of 4.14 QALYs over the 5 years. This compared with an estimated cost of VNS over the 5 years of $50,742.96 for a gain of 3.89 QALYs, a strategy which was dominated by the less costly and more effective strategy of a third AED.[88] In a secondary analysis for a child who had failed to respond to 3 AEDs, VNS again was dominated, with the ketogenic diet costing an estimated $16,227.58 with a QALY gain of 3.60 compared with a VNS estimated cost of $53,511.68 for a QALY gain of 3.89.[88]

Purser et al.[89] estimated the budget impact and effect on health outcomes of expanding the use of VNS in children aged 12 and older with drug-resistant epilepsy with partial-onset seizures. The perspective was that of a managed care organization.[89] On average, VNS resulted in an estimated net cost savings of $77,480 per patient over 5 years, a 21.5% reduction in costs compared with AEDs alone.[89]

Patients with VNS had an estimated reduction in costs associated with seizure frequency of $127,554 per patient over 5 years compared with patients with AEDs alone.[89] Seizure-related hospitalizations were the main cost driver, resulting in an estimated cost reduction of $118,925 per patient over 5 years for patients with VNS compared with AEDs alone.[89] Results were most sensitive to per-person hospitalization cost per year, with and without VNS in years 3 to 5 after VNS device placement; however, VNS remained cost saving over 5 years. The initial cost of the VNS device, placement, and programming was estimated to be offset 1.7 years after VNS device placement.[89]

Depression

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

Summary

Epilepsy – Effectiveness

High-Stimulation VNS vs. Low-Stimulation VNS

- High-stimulation VNS was associated with more individuals having a 50% or more reduction in seizure frequency than low-stimulation VNS (low-quality evidence, based on 3 RCTs; Table 7).
- High-stimulation VNS was more effective in reducing the mean seizure frequency than low-stimulation VNS (very-low-quality evidence, based on 1 RCT; Table 7).
- High-stimulation and low-stimulation VNS were both associated with very low rates of seizure freedom (low-quality evidence, based on 2 RCTs; Table 7).

VNS vs. TAU or Ongoing Medication

- VNS and TAU or ongoing medication were associated with similar rates of response, defined as a 50% or more reduction in seizures (low-quality evidence, based on 1 RCT; Table 7).

- VNS was more effective in reducing seizure frequency than TAU or ongoing medication (very-low-quality evidence, based on 4 NRSs; Table 7).
- VNS was not associated with higher rates of seizure freedom than TAU or ongoing medication (very-low-quality evidence, based on 4 NRSs; Table 7).

VNS vs. Surgery

- VNS was similarly effective as surgery in reducing seizure frequency, but this was not consistent across studies (very-low-quality evidence, based on 4 NRSs; Table 7).
- VNS was less effective in reducing seizure freedom than surgery, but this was not consistent across studies (very-low-quality evidence, based on 5 NRSs; Table 7).

VNS vs. Responsive Neurostimulation

- VNS and responsive neurostimulation appear similarly effective in reducing seizure frequency, but this was not consistent across studies (very-low-quality evidence, based on 2 NRSs; Table 7).
- VNS and responsive neurostimulation appear similarly effective in terms of seizure freedom, but results are not consistent (very-low-quality evidence, based on 2 NRSs; Table 7).

High-Stimulation tVNS vs. Low-Stimulation tVNS

- High-stimulation tVNS and low-stimulation tVNS had similar rates of response, defined as a 50% reduction or more in seizure frequency (very-low-quality evidence, based on 1 RCT; Table 9)
- High-stimulation tVNS and low-stimulation tVNS had similar rates of seizure freedom (low-quality evidence, based on 1 RCT; Table 9).
- High-stimulation tVNS and low-stimulation tVNS had similar seizure severity scores (low-quality evidence, based on 1 RCT; Table 9).

Epilepsy – Harms

High-Stimulation VNS vs. Low-Stimulation VNS

High-stimulation VNS was associated with:

- Similar number of withdrawals as low-stimulation VNS (very-low-quality evidence, based on 3 RCTs; Table 8)
- Higher levels of voice alteration or hoarseness than low-stimulation VNS (moderate-quality evidence, based on 2 RCTs; Table 8)
- Similar rates of cough as low-stimulation VNS (very-low-quality evidence, based on 2 RCTs; Table 8)
- Higher rates of dyspnea than low-stimulation VNS (low-quality evidence, based on 2 RCTs; Table 8)
- Similar rates of pain as low-stimulation VNS (very-low-quality evidence, based on 2 RCTs; Table 8)
- Similar rates of paresthesias as low-stimulation VNS (very-low-quality evidence, based on 2 RCTs; Table 8)
- Similar rates of nausea as low-stimulation VNS (very-low-quality evidence, based on 2 RCTs; Table 8)

- Similar rates of headache as low-stimulation VNS (very-low-quality evidence, based on 2 RCTs; Table 8)

VNS vs. TAU

VNS was associated with:

- Similar number of withdrawals as TAU (low-quality evidence, based on 1 RCT; Table 8)
- Similar levels of voice alteration or hoarseness as TAU (very-low-quality evidence, based on 1 RCT; Table 8)
- Similar rates of pain as TAU (very-low-quality evidence, based on 1 RCT; Table 8)
- Similar rates of paresthesias as TAU (very-low-quality evidence, based on 1 RCT; Table 8)
- Similar rates of headache as TAU (very-low-quality evidence, based on 1 RCT; Table 8)

Based on 1 registry study, laryngeal symptoms (including hoarseness and coughing) and local dysesthesias related to VNS use tended to decrease over time while rates of high-lead impedance tended to increase. Other adverse events, such as cardiac or respiratory complications and local infections, were low at all time points.

High-Stimulation tVNS vs. Low-Stimulation tVNS

High-stimulation tVNS, when compared with low-stimulation tVNS, had:

- Similar number of withdrawals (very-low-quality evidence, based on 1 RCT; Table 10)
- Similar rates of pain (very-low-quality evidence, based on 1 RCT; Table 10)
- Similar rates of nausea (very-low-quality evidence, based on 1 RCT; Table 10)
- Similar rates of headache (very-low-quality evidence, based on 1 RCT; Table 10)

No participants in either group reported coughing or hoarseness (low-quality evidence, based on 1 RCT; Table 10).

Epilepsy – Economic Impact and Cost-effectiveness

VNS vs. TAU or Ongoing Medication

- VNS was more costly and less effective than other strategies for children with drug-resistant tuberous sclerosis complex who have not responded to 2 or 3 AEDs (very-low-quality evidence, based on 1 cost-utility study in this specific population; Table 11).
- VNS was associated with a reduction in costs over 5 years compared with AEDs alone (very-low-quality evidence, based on 1 budget impact study; Table 11).

Depression - Effectiveness

High-stimulation VNS vs. Low-stimulation VNS

- High-stimulation VNS was not associated with reduced depression severity (low-quality evidence, based on 1 RCT; Table 15).
- High-stimulation VNS was not associated with lower rates of suicide or attempted suicide (very-low-quality evidence, based on 1 RCT; Table 15).
- High-stimulation had higher rates of response, defined as 50% MADRS reduction, compared with low-stimulation VNS (low-quality evidence, based on 1 RCT; Table 15).

VNS vs. Sham VNS

- VNS was not associated with reduced depression severity, compared with sham VNS (moderate-quality evidence, based on 1 RCT; Table 15).
- VNS was not associated with lower rates of suicides, compared with sham VNS (very-low-quality evidence, based on 1 RCT; Table 15).
- VNS and sham VNS had similar rates of response, defined as 50% MADRS reduction (very-low-quality evidence, based on 1 RCT; Table 15).

VNS vs. TAU

- VNS with TAU was more effective in reducing depression symptoms than TAU alone (very-low-quality evidence, based on 1 NRS; Table 15).
- VNS with TAU may be associated with higher rates of response than TAU alone (very-low-quality evidence, based on 1 NRS; Table 15).
- VNS may be associated with higher rates of attempted suicide or self-inflicted injury, but the evidence is very uncertain and may reflect greater severity of depression in the VNS group (very-low-quality evidence, based on 1 NRS; Table 15).
- VNS may be associated with lower mortality rates, but study results are not consistent (very-low-quality evidence, based on 2 NRS; Table 15).

tVNS vs. Sham tVNS

- tVNS may be associated with meaningful changes in depression when compared with sham tVNS; however, this effect was not consistently reported across different measurement scales (low-quality evidence, based on 1 RCT; Table 17).

Depression – Harms

High-Stimulation VNS vs. Low-Stimulation VNS

High-stimulation and low-stimulation VNS have:

- Similar number of withdrawals (very-low-quality evidence, based on 1 RCT; Table 16)
- Similar levels of voice alteration or hoarseness (low-quality evidence, based on 1 RCT; Table 16)
- Similar rates of cough (very-low-quality evidence, based on 1 RCT; Table 16)
- Similar rates of dyspnea (low-quality evidence, based on 1 RCT; Table 16)
- Similar rates of pain (low-quality evidence, based on 1 RCT; Table 16)
- Similar rates of paresthesias (very-low-quality evidence, based on 1 RCT; Table 16)
- Similar rates of nausea (very-low-quality evidence, based on 1 RCT; Table 16)
- Similar rates of headache (very-low-quality evidence, based on 1 RCT; Table 16)

VNS vs. Sham VNS

VNS, when compared with sham VNS, has:

- Similar number of withdrawals (very-low-quality evidence, based on 1 RCT; Table 16)
- Higher levels of voice alteration or hoarseness (moderate-quality evidence, based on 1 RCT; Table 16)
- Higher levels of cough (moderate-quality evidence, based on 1 RCT; Table 16)
- Similar levels of dyspnea (low-quality evidence, based on 1 RCT; Table 16)

- Similar rates of pain (low-quality evidence, based on 1 RCT; Table 16)
- Similar rates of paresthesias (very-low-quality evidence, based on 1 RCT; Table 16)
- Similar rates of nausea (very-low-quality evidence, based on 1 RCT; Table 16)

VNS vs. TAU

VNS has higher completion rates than TAU (very-low-quality evidence, based on 1 NRS; Table 16).

tVNS vs. Sham tVNS

It is not clear what adverse events are associated with tVNS, when compared with sham tVNS, (very-low-quality evidence, based on 1 RCT; Table 18).

Depression - Economic Impact and Cost-effectiveness

We did not identify any studies reporting on economic outcomes related to the use of VNS or tVNS for depression.

FDA Reported Harms for Epilepsy and Depression

The types of adverse events reported to the FDA appear similar to those reported in our eligible studies for epilepsy and depression.

Recalls documented in the Medical Device Recall database included errors in impedance measurements, unintended warning messages, miscalculations resulting in inappropriate VNS stimulation (higher and lower levels of stimulation than expected), reductions in device and battery longevity, and lead fractures (Appendix G).

In December 2019, the FDA issued a Class I recall, the most serious type of recall, where problems with the recalled devices may cause serious injuries or death.[90] The FDA reported that LivaNova is recalling the VNS Therapy SenTiva Generator System due to an unintended reset error that causes the system to stop delivering VNS therapy.[90] If device replacement is needed, there is a risk associated with additional surgery to replace the generator.[90] The FDA issued guidance to patients and health care providers on actions they should take to ensure the risk of serious injury or death is minimized. [90]

Clinical Practice Guidelines

Epilepsy

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

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

The fair-methodological-quality guideline from the Task Force Report for the ILAE Commission of Pediatrics also recommended that infants with medically refractory seizures who are not suitable candidates for epilepsy surgery may be considered for VNS.[95] However, the Task Force did note there were insufficient data to conclude if there is a benefit from intervention with VNS in infants with seizures and the recommendation was therefore based on expert opinion and standard practice, including receiving optimal level of care at specialist facilities.[95]

Recommendations from the guidelines assessed as poor methodological quality[91,92,96] also support the use of VNS for adults and children who do not achieve adequate benefit from other epilepsy therapies, such as changes in AEDs, surgery, and particularly for children, the ketogenic diet. Only 1 guideline explicitly recommended against the use of tVNS for drug-resistant epilepsy.[92]

Table 20. Clinical Practice Recommendations on VNS for Epilepsy

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

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

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

Depression

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

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

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

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

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

Selected Payer Coverage Determinations

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

The NCD currently states that[2]:

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

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

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

Each of the 3 private payers that we reviewed, Aetna, Cigna, and, Regence, had coverage policies for VNS.[120-122]

Aetna considers VNS to be medically necessary for[120]:

- Members with focal seizures who remain refractory to optimal antiepileptic medications and/or surgical intervention, or who have debilitating side effects from antiepileptic medications, and who have no history of a bilateral or left cervical vagotomy
- Members with Lennox-Gastaut syndrome who remain refractory to optimal antiepileptic medications, and/or surgical intervention, or who have debilitating side effects from antiepileptic medications, and who have no history of a bilateral or left cervical vagotomy

Aetna considers replacement or revision VNS medically necessary if the original system or magnet met the criteria as medically necessary and is no longer under warranty and cannot be repaired.[120]

Aetna considers tVNS to be experimental and investigational for treatment of epilepsy, citing a lack of evidence.[120] Aetna also considers VNS and tVNS to be experimental and investigational for the treatment of depression, citing a lack of evidence.[120]

Cigna considers VNS to be medically necessary for the treatment of medically intractable seizures when there is failure, contraindication or intolerance to all suitable medical and

pharmacological management.[121] Cigna also considers the replacement or revision of a VNS as medically necessary when a previously implanted VNS or leads are no longer functioning appropriately.[121] Like other commercial payers, Cigna considers VNS as experimental, investigational, or unproven for any other indication including, but not limited to, refractory depression.[121] Cigna also considered tVNS as experimental, investigational, or unproven for any indication.[121]

Regence considers VNS to be medically necessary for members with medically refractory seizures who have tried and been unresponsive to, or intolerant of, at least 2 AEDs.[122] Revision or replacement of VNS and its components is also considered medically necessary.[122] Regence considers the use of VNS for all other indications including depression, and the use of tVNS, as investigational.[122]

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

Ongoing Studies

We searched the ClinicalTrials.gov database for ongoing studies related to VNS for epilepsy or depression (Appendix I). We identified 3 ongoing studies (randomized and nonrandomized) that would be eligible for this evidence review (Table 22).[103-105] One ongoing study is in epilepsy and two are in depression. The RECOVER trial, NCT03887715,[105] is currently the only CMS-approved RCT for VNS in depression.[2]

Table 22. Included Ongoing Studies of VNS for Epilepsy and Depression

NCT Number Study Name Study Type	Participants	Treatment Groups	Outcomes	Estimated Enrollment	Primary Completion Date
Epilepsy					
NCT03529045[103] CORE-VNS Prospective registry	Adults and children with drug-resistant epilepsy	VNS only	• Seizure frequency • Seizure severity • Quality of life • Sleep • AED use • Rescue drug use • ED visits • Hospitalization	2,000	December 2026
Depression					
NCT03320304[104] RESTORE-LIFE Prospective registry	Adults with difficult-to-treat depression	VNS only	• Depression • Duration of response • Mania • Quality of life • Functional activity (e.g., work) • Suicidality • Antidepressant treatment • Adverse events • Cognition • Anxiety	500	December 2023
NCT03887715[105] RECOVER RCT	Adults with TRD	VNS Sham VNS	• Depression • Adverse events • Disability • Quality of life • Global improvement • Suicidality	6,800	August 2022

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

Conclusions

Epilepsy

High-stimulation VNS is associated with reduced seizure frequency when compared with low-stimulation VNS (low- to very-low-quality evidence). VNS is also associated with similar reductions in seizure frequency to ongoing medication or surgery (very-low-quality evidence). People with a VNS implant may experience changes in their voice or hoarseness and some breathlessness, but in general, the rates of adverse effects are no different to low-stimulation VNS or TAU (moderate- to very-low-quality evidence). Adverse events, such as hoarseness and

coughing, are often transient and tend to decrease over time. In some cases, adverse events can be minimized through adjustment of the stimulation parameters.

In 2017, the FDA considered new evidence for the expanded use of VNS for epilepsy in young children aged 4 and older.[1] The prior approval was limited to children aged 12 and older.[1] Based on an analysis of younger and older children and young adults in the pivotal trials used for the initial approval, a Japanese registry, and the Cyberonics Post-Market Surveillance database, the FDA concluded that[1]:

- VNS is an effective and safe treatment for the reduction of partial onset seizures in pediatric patients 4 to 11 years of age with refractory epilepsy.
- Based on the Bayesian hierarchical model, the 12-month responder rate for pediatric patients 4 to 11 years of age with partial onset seizures in the Japan post-approval study is 39% (95% credible interval, 28% to 52%).
- There were no unanticipated adverse device effects observed in pediatric patients 4 to 11 years of age. However, infection and extrusion of lead had a statistically greater incidence rate in patients 4 to 11 years of age.
- Younger patients may have a greater risk for wound infection when compared to adolescents and adults; therefore, the importance of monitoring for site infection as well as the avoidance of manipulation of the surgical site post implant in children should be emphasized.
- Overall, treatment-emergent adverse events in patients 4 to 11 years of age were consistent with patients ≥ 12 years of age treated with VNS, and no new risks were identified.

The FDA has also issued guidance on how to increase the availability of safe and effective pediatric devices by outlining when it may be appropriate to leverage existing clinical data to support pediatric device indications and labeling.[123] Principles of extrapolation from data in adult populations include[123]:

- Relevancy
  - Does the condition occur in a pediatric population?
  - Is there an endpoint present in the existing data source that measures device effects relevant to the intended pediatric population?
- Similarity of response
  - Is the device implanted or in contact with the body, and if so, does either the location or duration of implantation differ between the adult and intended pediatric population in such a way that the safety or effectiveness of the device could be impacted in a clinically meaningful way?
  - Are there differences in device characteristics between pediatric and adult use that could impact either device safety or effectiveness in the pediatric population in a clinically meaningful way?
  - Are there characteristics unique to the intended pediatric population that could impact either the effectiveness or safety of the device when used in the pediatric population in a clinically meaningful way?
  - Are there differences in disease characteristics between the adult and pediatric populations that could impact either device safety or effectiveness in the pediatric population in a clinically meaningful way?

- Are there other differences between the adult and pediatric populations that could impact either device effectiveness or safety in the pediatric population in a clinically meaningful way?

The FDA also notes that factors that could limit the extrapolation of any adult data include, but are not limited to, the following:

- There is little knowledge of the disease or condition in pediatrics.
- The device is not FDA-approved or -cleared for adults.
- Endpoints cannot be directly borrowed.
- Statistical models cannot account for differences.
- Human factors and growth can affect safety in pediatric patients.
- Appropriate labeling cannot be written for the pediatric population targeted.
- The practice of medicine has changed since the device was initially approved to such an extent that historical data would likely be different than prospectively-collected data.
- Appropriate risk mitigation cannot be assured.

The guidance from the FDA[123] may be a useful framework within which to consider the evidence in adults presented in this report for proposed and expanded indications in the pediatric population.

In practice, people with drug-resistant epilepsy may have tried all the available and appropriate AEDs, and may also not be suitable for resective surgery after a comprehensive assessment. In virtually all identified clinical practice guidelines, VNS is recommended as a treatment option for adults and children who are refractory to antiepileptic medication, but are not suitable for resective surgery. The NCD for Medicare currently states that[2]:

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

Coverage polices from 3 commercial payers are also consistent in approving coverage for the management of medically-refractory seizures, as well as any necessary revision or replacement of the implant or battery. All of the commercial payers we reviewed consider the use of tVNS as experimental and investigational.

However, VNS may not be cost-effective in subgroups of people with specific types of seizure disorders (e.g., drug-resistant tuberous sclerosis complex) but the wider cost-effectiveness in patients 4 years of age and older with partial onset seizures that are refractory to AEDs remains unclear. One analysis estimated that VNS would result in reduced costs over 5 years compared with AEDs alone, but our confidence in this estimate was very low, and there is a lack of cost-effectiveness evidence for longer durations of treatment.

We identified 1 RCT which did not demonstrate any benefit of tVNS for epilepsy, and the guidelines and coverage policies which mentioned tVNS were not supportive of its use for seizure disorders.

Depression

High-stimulation VNS is associated with an increased response rate (as measured on the MADRS) when compared with low-stimulation VNS (low-quality evidence), but other outcomes, such as reduced depression severity using other scales and suicide deaths or attempts, are not different between stimulation groups (low- to very-low-quality evidence). VNS with TAU reduced depressive symptoms more than TAU alone (very-low-quality evidence); however, the difference was small and may not be clinically meaningful. VNS with TAU also resulted in higher rates of response compared with TAU alone (very-low-quality evidence). Other outcomes were no different between groups (sham VNS or TAU) or were inconsistent, making it difficult to draw robust conclusions about the effectiveness of VNS for depression in adults. As with the use of VNS for epilepsy, patients using the VNS implant may experience voice alteration or hoarseness and coughing related to the use of VNS (moderate- to very-low-quality evidence).

Most guidelines either recommend against the use of VNS for depression, citing a lack of evidence and calling for more research, or did not make any specific recommendations for or against the use of tVNS for depression. However, 1 guideline did recommend VNS as a third-line treatment, after repetitive transcranial magnetic stimulation (first-line treatment) and ECT (second-line treatment) for adults with MDD.

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

Overall, there is a high level of agreement across the coverage determinations, with VNS for depression not being covered by any of the 3 commercial payers reviewed for this report.

We identified 1 RCT that did not demonstrate any consistent evidence of a benefit of tVNS for depression, and the guidelines and coverage policies that mentioned tVNS were not supportive of its use for depression in adults.

We did not identify any studies reporting on economic outcomes related to the use of VNS or tVNS for depression.

FDA-Reported Harms for Epilepsy and Depression

The types of adverse events reported to the FDA appear similar to those reported in our eligible studies for epilepsy and depression.

Recalls documented in the Medical Device Recall database included errors in impedance measurements, unintended warning messages, miscalculations resulting in inappropriate VNS stimulation (both higher and lower levels of stimulation than expected), reductions in device and battery longevity, and lead fractures (Appendix G).

In December 2019, the FDA issued a Class I recall, the most serious type of recall, where problems with the recalled devices may cause serious injuries or death.[90] The FDA reported that LivaNova is recalling the VNS Therapy SenTiva Generator System due to an unintended reset error that causes the system to stop delivering VNS therapy.[90] If device replacement is needed, there is a risk associated with additional surgery to replace the generator.[90] The FDA issued guidance to patients and health care providers on actions they should take to ensure the risk of serious injury or death is minimized.[90]

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

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Appendix A. Search Strategy

Databases

- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other NonIndexed Citations and Daily: from 1946 to October 10, 2019
- Cochrane Library databases (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials): from database inception to October 10, 2019
- PsycINFO: from 1806 to October 10, 2019

Search Terms for Ovid MEDLINE

1. Vagus Nerve Stimulation/

2. ((vagal or vagus) adj3 (

* or electrosimulat* or electro-simulat*)).ti,ab,kw,kf.

3. ((vagal or vagus) adj2 nerve).ti,ab,kw,kf.

4. or/1-3

5. exp Epilepsy/

6. epileps*.ti,ab,kw,kf.

7. seizure disorder?.ti,ab,kw,kf.

8. or/5-7

9. exp Depressive Disorder, Treatment-Resistant/

10. Depressive Disorder/

11. ((therapy-resistant or "therapy resistant" or treatment-resistant or "treatment resistant") adj3 (depress* or mood disorder*)).ti,ab,kw,kf.

12. ((refractory or major) adj2 depress*).ti,ab,kw,kf.

13. or/9-12

14. 4 and (8 or 13)

15. limit 14 to english language

16. animals/ not (animals/ and humans/)

17. 15 not 16

Appendix B. Additional Methods

Risk of Bias Assessment: Randomized Controlled Trials

Domain	Domain Elements The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate*, or *Low* based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.
Randomization	• An appropriate method of randomization is used to allocate participants or clusters to groups, such as a computer random number generator • Baseline characteristics between groups or clusters are similar
Allocation Concealment	• An adequate concealment method is used to prevent investigators and participants from influencing enrollment or intervention allocation
Intervention	• Intervention and comparator intervention applied equally to groups • Co-interventions appropriate and applied equally to groups • Control selected is an appropriate intervention
Outcomes	• Outcomes are measured using valid and reliable measures • Investigators use single outcome measures and do not rely on composite outcomes, or the outcome of interest can be calculated from the composite outcome • The trial has an appropriate length of follow-up and groups are assessed at the same time points • Outcome reporting of entire group or subgroups is not selective
Masking (Blinding) of Investigators and Participants	• Investigators and participants are unaware (masked or blinded) of intervention status
Masking (Blinding) of Outcome Assessors	• Outcome assessors are unaware (masked or blinded) of intervention status
Intention to Treat Analysis	• Participants are analyzed based on random assignment (intention-to-treat analysis)
Statistical Analysis	• Participants lost to follow-up unlikely to significantly bias the results (i.e., complete follow-up of ≥ 80% of the participants overall and nondifferential, ≤ 10% difference between groups) • The most appropriate summary estimate (e.g., risk ratio, hazard ratio) is used • Paired or conditional analysis used for crossover RCT • Clustering appropriately accounted for in a cluster-randomized trial (e.g., use of an intraclass correlation coefficient)
Other Biases (as appropriate)	List others in table footnote and describe, such as: • Sample size adequacy • Interim analysis or early stopping • Recruitment bias, including run-in period used inappropriately • Use of unsuitable crossover intervention in a crossover RCT
Interest Disclosure	• Disclosures of interest are provided for authors/funders/commissioners of the study • Interests are unlikely to significantly affect study validity
Funding	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Abbreviation. RCT: randomized controlled trial.

Risk of Bias Assessment: Nonrandomized Studies

Domain	Domain Elements The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate* or *Low*, based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.
Participant Selection	For cohort studies: • The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation, or statistical adjustment is used appropriately to achieve this • The study indicates how many of the people asked to take part did so, in each of the groups being studied • The likelihood that some eligible participants might have the outcome at the time of enrolment is assessed and taken into account in the analysis • Fewer than 20% of individuals or clusters in each arm of the study dropped out before the study was completed For case-control studies: • Cases and controls are clearly specified and defined, with the inclusion and exclusion criteria applied appropriately • Cases may be selected by meeting inclusion criteria, controls may be selected by meeting inclusion criteria and then being matched to cases • Sampling selection (ratio of cases to control) is justified • Cases and controls selected from the same population and same timeframe. When not all cases and controls are selected from the same population, they are randomly selected • Among cases, investigators confirm that the exposure occurred before the development of the disease being studied and/or the likelihood that some eligible participants might have the outcome at the time of enrolment is assessed and taken into account in the analysis
Intervention	• The assessment of exposure to the intervention is reliable • Exposure level or prognostic factors are assessed at multiple times across the length of the study, if appropriate • For case-control studies assessors of (intervention) exposure status are unaware (masked or blinded) to the case or control status of participants there is a method to limit the effects of recall bias on the assessment of exposure to the intervention
Control	• Control condition represents an appropriate comparator
Outcome	• There is a precise definition of the outcomes used • Outcomes are measured using valid and reliable measures, evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable • Investigators use single outcome measures and do not rely on composite outcomes, or the outcome of interest can be calculated from the composite outcome • The study has an appropriate length of follow-up for the outcome reported and groups are assessed at the same time points • Outcome reporting of entire group or subgroups is not selective • When patient-reported outcomes are used there is a method for validating the measure

Domain	Domain Elements The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate* or *Low*, based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.
Masked Outcome Assessment	• The assessment of outcome(s) is made blind to exposure status. Where outcome assessment blinding was not possible, there is recognition that knowledge of exposure status could have influenced the assessment of outcome • For case-control study: assessors of exposure status are unaware (masked or blinded) of the case or control status of participant)
Confounding	• The main potential confounders are identified and taken into account in the design and analysis of the study
Statistical Analysis	• Comparison is made between full participants and those who dropped out or were lost to follow-up, by exposure status • If the groups were not followed for an equal length of time, the analysis was adjusted for differences in the length of follow-up • All major confounders are adjusted for using multiple variable logistic regression or other appropriate statistical methods • Confidence intervals (or information with which to calculate them) are provided • For case-control studies that use matching, conditional analysis is conducted or matching factors are adjusted for in the analysis
Other Biases (as appropriate)	• List others in table footnote and describe, e.g., • Sample size adequacy
Interest Disclosure	• Disclosures of interest are provided for authors/funders/commissioners of the study • Interests are unlikely to significantly affect study validity
Funding Source	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Risk of Bias Assessment: Economic Studies

Domain	Domain Elements The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate*, or *Low* based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.
Target Population	• Target population and care setting described • Describe and justify basis for any target population stratification, identify any a priori identifiable subgroups • If no subgroup analyses were performed, justify why they were not required
Perspective	• State and justify the analytic perspective (e.g., societal, payer, etc.)
Time Horizon	• Describe and justify the time horizon(s) used in the analysis
Discount Rate	• State and justify the discount rate used for costs and outcomes
Comparators	• Describe and justify selected comparators • Competing alternatives appropriate and clearly described
Modelling	• Model structure (e.g., scope, assumptions made) is described and justified • Model diagram provided, if appropriate • Model validation is described (may involve validation of different aspects such as structure, data, assumptions, and coding and different validation models such as comparison with other models) • Data sources listed and assumptions for use justified • Statistical analyses are described
Effectiveness	• Estimates of efficacy/effectiveness of interventions are described and justified • The factors that are likely to have an impact on effectiveness (e.g., adherence, diagnostic accuracy, values, and preferences) are described and an explanation of how they were factored into the analysis is included • The quality of evidence for the relationship between the intervention and outcomes, and any necessary links, is described
Outcomes	• All relevant outcomes are identified, measured, and valued appropriately (including harms/adverse events) for each intervention, and the justification for information/assumptions is given • Any quality of life measures used in modelling are described and their use justified • Any other outcomes that were considered, but rejected, are described with the rationale for rejection • Ethical and equity-related outcomes are considered and included when appropriate
Resource Use/Costs	• All resources used are identified, valued appropriately, and included in the analyses • Methods for costing are reporting (e.g., patient level) • Resource quantities and unit costs are both reported • Methods for costing time (e.g., lost time, productivity losses) are appropriate and a justification is provided if time costs are not considered
Uncertainty	• Sources of uncertainty in the analyses are identified and justification for probability distributions used in probabilistic analyses are given • For scenario analyses, the values and assumptions tested are provided and justified

Domain	Domain Elements The elements included in each domain are assessed and rated as *Yes*, *No*, *Unclear*, or *Not Applicable* based on performance and documentation of the individual elements in each domain. The overall risk of bias for the study is assessed as *High*, *Moderate*, or *Low* based on assessment of how well the overall study methods and processes were performed to limit bias and ensure validity.
Results	• All results are presented in a disaggregated fashion, by component, in addition to an aggregated manner • All results are presented with undiscounted totals prior to discounting and aggregation • Natural units are presented along with alternative units (e.g., QALYs) • The components of the incremental cost-effectiveness ratio (ICER) are shown (e.g., mean costs of each intervention in numerator and mean outcomes of each intervention in denominator) • Results of scenario analyses, including variability in factors such as practice patterns and costs, are reported and described in relation to the reference (base) case
Interest Disclosure	• Disclosures of interest are provided for authors/funders/commissioners of the study • Interests are unlikely to significantly affect study validity
Funding Source	• There is a description of source(s) of funding • Funding source is unlikely to have a significant impact on study validity

Abbreviations. ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Risk of Bias Assessment: Clinical Practice Guidelines

Domain	Domain Elements Assessment indicates how well the guideline methodology and development process were performed to limit bias and ensure validity for elements in domain (each domain rated as *Good*, *Fair*, or *Poor* overall based on performance and documentation of elements)
Rigor of Development: Evidence	• Systematic literature search that meets quality standards for a systematic review (i.e., comprehensive search strategy with, at a minimum, 2 or more electronic databases) • The criteria used to select evidence for inclusion is clear and appropriate • The strengths and limitations of individual evidence sources is assessed and overall quality of the body of evidence assessed
Rigor of Development: Recommendations	• Methods for developing recommendations clearly described and appropriate • There is an explicit link between recommendations and supporting evidence • The balance of benefits and harms is considered in formulating recommendations • The guideline has been reviewed by external expert peer reviewers • The updating procedure for the guideline is specified in the guideline or related materials (e.g., specialty society website)
Editorial Independence	• There is a description of source(s) of funding and the views of the funder(s) are unlikely to have influenced the content or validity of the guideline • Disclosures of interests for guideline panel members are provided and are unlikely to have a significant impact on the overall validity of the guideline (e.g., a process for members to recuse themselves from participating on recommendations for which they have a significant conflict is provided)
Scope And Purpose	• Objectives specifically described • Health question(s) specifically described • Target population(s) for guideline recommendations is specified (e.g., patients in primary care) and target users for the guideline (e.g., primary care clinicians)
Stakeholder Involvement	• Relevant professional groups represented • Views and preferences of target population(s) sought (e.g. clinicians and patients)
Clarity And Presentation	• Recommendations are specific and unambiguous • Different management options are clearly presented • Key recommendations are easily identifiable
Applicability	• Provides advice and/or tools on how the recommendation(s) can be put into practice • Description of facilitators and barriers to its application • Potential resource implications considered • Criteria for implementation monitoring, audit, and/or performance measures based on the guideline are presented

Appendix C. Evidence Tables

Table C1. Study Characteristics for Randomized Controlled Trials

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
Epilepsy						
Bauer et al., 2016[79] cMPsE02 9 sites in Germany and 1 site in Austria	To assess the efficacy and safety of 20 weeks of tVNS in patients with drug-resistant epilepsy RCT 20 weeks of active treatment	Inclusion criteria (must meet all): aged 18 to 65; diagnosis of epilepsy with focal and/or generalized seizures; ≥ 3 seizures per month; not more than 21 consecutive seizure-free days; on a stable regimen of ≤ 3 AEDs for at least 5 weeks; maintenance of AED treatment during the study Exclusion criteria (excluded if any criteria met): > 1 episode of status epilepticus within 6 months prior to study enrollment; current or prior treatment with invasive VNS or DBS; prior ablative epilepsy surgery; history of nonepileptic seizures; major psychiatric disorders;	Total N = 76, comprising 37 in the high-stimulation group and 39 in the low-stimulation group Sex: 20 of 27 (54%) female, high-stimulation; 25 of 29 (64%) female, low-stimulation Mean age (SD): 40.1 years (12.7), high-stimulation; 37.5 years (12.2), low-stimulation Type of seizures: 28 of 37 (76%) partial, 9 of 37 (24%) primarily generalized, high-stimulation; 26 of 39 (67%) partial, 13 of 39 (33%) primarily generalized, low-stimulation Mean duration of epilepsy (SD): 23.0 years (15.4), high-	• High-stimulation tVNS	• Low-stimulation tVNS	• Seizure frequency • Seizure freedom • Seizure severity • Mood or cognitive changes • Quality of life • Harms

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
		deteriorating neurological or medical conditions and/or relevant cardiac diseases	stimulation; 24.2 years (13.8), low-stimulation On any AED: 25 of 37 (68%), high-stimulation; 26 of 29 (67%), low-stimulation			
Handforth et al., 1998[80] Dodrill et al., 2001[49] 20 sites in the U.S. E05	To compare the efficacy and safety of presumably therapeutic (high) VNS with less (low) stimulation RCT 12 weeks	Inclusion criteria (must meet all): age 12 to 65; diagnosis of medically refractory partial-onset seizures; at least 6 partial-onset seizures involving alteration of consciousness (complex partial or secondarily generalized convulsions) over 30 days, with no more than 21 days between seizures; aged 12 to 65; use acceptable contraception if female and fertile; take 1 to 3 AEDs on a stable regimen for at least 1 month or 5 half-lives plus 2 weeks (whichever	Total N = 198, comprising 95 in the high-stimulation group and 103 in the low-stimulation group Sex: 46 of 95 (48.4%) female, high-stimulation; 59 of 103 (57.3%), low-stimulation Mean age (range): 32.1 years (13 to 54), high-stimulation; 34.2 years (15 to 60), low-stimulation Race or ethnicity: 85 of 95 (89.5%) White, 7 of 95 (7.4%) Hispanic, 3 of 95 (3.1%) other, high-stimulation; 86 of 103 (83.5%) White, 10 of 103 (9.7%) Hispanic,	• High-stimulation VNS	• Low-stimulation VNS	• Seizure frequency • Seizure freedom • Treatment withdrawal • Mood or cognitive changes • Quality of life • Harms • Failure rate

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
		was longer) before study entry Exclusion criteria (excluded if any criteria met): deteriorating neurologic or medical conditions; pregnancy; cardiac or pulmonary disease; active peptic ulcer; history of nonepileptic seizures; > 1 episode of status epilepticus in the previous 12 months; prior cervical vagotomy; prior VNS; prior brain stimulation; resective epilepsy surgery; inability to perform pulmonary function tests	7 of 103 (6.8%) other, low-stimulation Mean total seizure frequency (SD): 1.59 (3.26), high-stimulation; 0.97 (1.13), low-stimulation Median total seizure frequency: 0.58, high-stimulation; 0.51, low-stimulation Mean partial seizure with alteration of awareness frequency (SD): 1.21 (1.96), high-stimulation; 0.83 (0.94), low-stimulation Median partial seizure with alteration of awareness frequency: 0.51, high-stimulation; 0.49, low-stimulation Mean number of AEDs at enrollment (SD): 2.2 (0.7), high-stimulation; 2.1 (0.7), low-stimulation			

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
			Mean number of AEDs tried and discontinued (SD): 5.0 (2.3), high-stimulation; 5.7 (2.5), low-stimulation Mean duration of epilepsy (range): 22.1 years (2 to 48), high-stimulation; 23.7 years (2 to 52), low-stimulation			
Klinkenberg et al., 2012[82] Klinkenberg et al., 2013[83] University medical center, Netherlands None	To evaluate the effects of VNS in children with intractable epilepsy on seizure frequency and severity and in terms of tolerability and safety RCT Up to 39 weeks of active treatment (20 weeks blinded)	Inclusion criteria (must meet all): medically refractory epilepsy despite adequate and stable AED concentrations; age 4 to 18 years; not eligible for epilepsy surgery Exclusion criteria (excluded if any criteria met): nonepileptic seizures; documented history of generalized status epilepticus in the previous 3 months; evidence of a progressive cerebral lesion, degenerative	Total N = 41, comprising 21 in the high-stimulation group and 20 in the low-stimulation group Sex: 48% female, high-stimulation; 40% female, low-stimulation Mean age (range): 10 years and 11 months (3 years and 10 month to 17 years and 8 months), high-stimulation; 11 years and 6 months (4 years and 2 month to 17 years and 2 months), low-stimulation	• High-stimulation VNS	• Low-stimulation VNS	• Seizure frequency • Seizure severity • Treatment withdrawal • Mood or cognitive changes • Quality of life • Harms

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
		disorder, or malignancy in the previous 5 years; presence of unstable medical disease (i.e. cardiovascular, hepatic, renal, musculoskeletal, gastrointestinal, metabolic, endocrine) in the previous 2 years; schizophrenia or any psychotic symptomatology; a high risk of complications (obstructive respiratory disease, gastric disorders, cardiac rhythm disorders); history of alcohol or drug abuse, or of psychiatric disorder requiring ECT or chronic use of major tranquillizers (neuroleptics, antidepressants) in the previous 6 months; regular treatment with antihistamines, metoclopramide, or central nervous	Mean age at onset (range): 2 years and 10 months (0 to 12 years), high-stimulation; 1 year and 8 months (0 to 5 years), low-stimulation Mean time since onset of epilepsy (range): 7 years and 8 months (2 to 16 years), high-stimulation; 9 years and 5 months (3 to 15 years) Median seizure frequency (range): 2.1 per day (0.1 to 53.7), high-stimulation; 0.9 per day (0.1 to 31.7), low-stimulation Mean number of AEDs ever used (range): 7.0 (5 to 10), high-stimulation; 7.3 (4 to 14), low-stimulation ILAE classification: 90% localization-related, 71% symptomatic, 19%			

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
		system-active compounds; treatment with an experimental drug during the previous 30 days	cryptogenic, 10% generalized, 0 idiopathic, 10% symptomatic, high-stimulation; 80% localization-related, 50% symptomatic, 30% cryptogenic, 20% generalized, 10% idiopathic, 10% symptomatic, high-stimulation			
Landy et al., 1993[51] University hospital, U.S. None	To determine whether variation of stimulation parameters is significant for seizure control RCT Minimum of 38 weeks	Inclusion criteria (must meet all): poorly controlled CPSs resistant to pharmacological treatment Exclusion criteria (excluded if any criteria met): none reported	Total N = 9, comprising 5 in the high-stimulation group and 4 in the low-stimulation group No patient characteristics were reported for the randomized subgroup	• High-stimulation VNS	• Low-stimulation VNS	• Seizure frequency • Seizure duration • Treatment withdrawal
Ryvlin et al., 2014[86] 28 sites in Europe and Canada NCT00522418, PuLsE	To evaluate whether VNS as adjunct to BMP superior to BMP alone in improving long-term	Inclusion criteria (must meet all): age 16 to 75; at least a 2-year history of focal seizures not adequately controlled by ongoing AED therapy; previous failure of at least 3	Total N = 112, comprising 48 in the VNS+BMP group and 48 in the BMP group for the efficacy analyses	• VNS+BMP	• BMP, defined as the individualized therapy judged optimal by investigators at each visit for each	• Seizure frequency • Treatment withdrawal • Quality of life • Harms

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
	health-related QoL RCT 12 months	AEDs used alone or in combination; treatment with at least 1 AED with a regimen that was stable for at least 1 month prior to study entry; at least 1 focal seizure with a motor component per month during the 2 months prior to study entry Exclusion criteria (excluded if any criteria met): psychogenic nonepileptic seizures ; genetic (idiopathic) generalized epilepsies	Sex: 50% female, VNS+BMP; 44% female, BMP Mean age (SD): 38 years (13), VNS+BMP; 41 years (11), BMP Mean age at onset of epilepsy (SD): 13 years (14), VNS+BMP; 16 years (14), BMP Etiology of epilepsy: 54% structural or metabolic, 46% unknown, VNS+BMP; 54% structural or metabolic, 46% unknown, VNS+BMP Median seizure frequency (range) per week: 5 (1 to 123), VNS+BMP; 4 (1 to 42), BMP Median number of AEDs (range): 3 (1 to 5), VNS+BMP; 3 (1 to 4), BMP Mean AED load (SD): 3.5 (1.17), VNS+BMP; 3.2 years (1.22), BMP		patient, which could include a change in dosage or type of AEDs (including withdrawal)	

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
Vagus Nerve Stimulation Group, 1995[87] Elger et al., 2000[50] 17 sites in the U.S., Canada, and Europe E03	To evaluate the efficacy and safety of adjunctive VNS in patients with poorly controlled partial seizures RCT 12 weeks of active treatment	Inclusion criteria (must meet all): medically intractable seizures defined as a frequency of ≥ 6 per month; predominantly partial seizure types; age 12 and older Exclusion criteria (excluded if any criteria met): progressive or unstable neurologic illness other than epilepsy; any unstable medical condition; pregnancy; use of > 3 AEDs at the time of study entry; use of an investigational AED at the time of study entry; ≥ 20% variation in any AED level at baseline	Total N = 114, comprising 54 (47%) in the high-stimulation group and 60 (53%) in the low-stimulation group Sex: 39% female, high-stimulation; 37% female, low-stimulation Mean age: 33.1 years, high-stimulation; 33.5 years, low-stimulation Mean number of seizures per day: 1.49 years, high-stimulation; 1.71 years, low-stimulation Median number of seizures per day: 0.73 years, high-stimulation; 0.82 years, low-stimulation Mean duration of epilepsy: 23.1 years, high-stimulation; 20.0 years, low-stimulation Mean number of AEDs: 2.09, high-	• High-stimulation VNS	• Low-stimulation VNS	• Seizure frequency • Seizure freedom • Harms • Reimplantation • Failure rate

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
			stimulation; 2.08, low-stimulation Type of seizures: 24 simple partial, 50 complex partial, 38 partial secondary generalized, high-stimulation; 25 simple partial, 58 complex partial, 33 partial secondary generalized, low-stimulation			
Depression						
Aaronson et al., 2013[78] 29 academic and clinical sites in the U.S. NCT00305565, D-21	To compare the safety and effectiveness of different stimulation levels of adjunctive VNS for the treatment of TRD RCT 12 months	Inclusion criteria (must meet all): 18 years of age or older; diagnosis of chronic (> 2 years) or recurrent (≥ 2 prior episodes) MDD or bipolar disorder; current diagnosis of MDE; history of failure to respond to ≥ 4 adequate dose/duration of antidepressant treatment trials from at least 2 different antidepressant treatment categories;	Total N = 310, comprising 107 in the high-stimulation group, 101 in the medium-stimulation group, and 102 in the low-stimulation group for efficacy analyses Sex: 68.2% female, high-stimulation; 68.3% female, medium-stimulation; 66.7% female, low-stimulation Mean age (SD): 47.4 years (10.8), high-stimulation; 47.2	• High-stimulation VNS • Medium-stimulation VNS	• Low-stimulation VNS	• Depression severity • Mortality • Suicidal ideation and severity • Response and duration of response • Remission and duration of remission • Anxiety • Treatment withdrawal • Harms

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
		minimum pre-study and baseline score of 24 on MADRS score with no greater than a 25% decrease in the MADRS score between the pre-study and baseline visits; currently receiving at least 1 antidepressant treatment (medication or ECT); a stable regimen of all current antidepressant treatments for a minimum of 4 weeks before the baseline visit; patients with bipolar disorder had to be receiving a mood stabilizer at baseline Exclusion criteria (excluded if any criteria met): history of any psychotic disorder; a history of rapid cycling bipolar disorder; clinically significant suicidal intent at the time of screening; history of	years (11.0), medium-stimulation; 49.1 years (10.5), low-stimulation Race or ethnicity: 97.2% Caucasian, high-stimulation; 95.0% Caucasian, medium-stimulation; 95.1% Caucasian, low-stimulation Mean age at onset (SD): 20.4 years (10.4), high-stimulation; 21.2 years (11.5), medium-stimulation; 19.3 years (11.0), low-stimulation Mean duration of illness (SD): 27.0 years (12.1), high-stimulation; 26.3 years (10.9), medium-stimulation; 29.8 years (12.1), low-stimulation Recurrent MDD: 66.7%, high-stimulation; 70.3%, medium-stimulation;			

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
		drug or alcohol dependence in the last 12 months; a current diagnosis of bipolar disorder mixed phase; history of borderline personality disorder; a history of previous VNS system implant; at high risk for surgery; currently enrolled in another investigational treatment study	74.5%, low-stimulation Single-episode MDD: 14.0%, high-stimulation; 9.9%, medium-stimulation; 5.9%, low-stimulation Bipolar I disorder: 14.0%, high-stimulation; 10.9%, medium-stimulation; 8.8%, low-stimulation Bipolar II disorder: 10.3%, high-stimulation; 8.9%, medium-stimulation; 10.8%, low-stimulation Mean length of current episode (SD): 9.3 years (12.2), high-stimulation; 8.8 years (8.9), medium-stimulation; 8.9 years (10.2), low-stimulation Prior ECT: 57.9%, high-stimulation; 52.5%, medium-stimulation; 59.8%, low-stimulation			

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
			Mean number of prior hospital admissions for mood disorders (SD): 2.8 (3.3), high-stimulation; 3.9 (6.1), medium-stimulation; 4.0 (5.1), low-stimulation Lifetime suicide attempts: 38.7%, high-stimulation; 43.6%, medium-stimulation; 54.9%, low-stimulation Baseline MADRS score (SD): 34.1 (4.4), high-stimulation; 33.9 (4.4), medium-stimulation; 34.2 years (5.2), low-stimulation Number of lifetime unsuccessful mood disorder treatments: 0 2 to 3, 2.8% 4 to 5, 97.2% 6 or more, high-stimulation; 0 2 to 3, 3.0% 4 to 5, 97.0% 6 or more, medium-stimulation; 2.0% 2 to 3, 1.0% 4 to			

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
			5, 97.1% 6 or more, low-stimulation Number of unsuccessful treatments in the current MDE: 3.8% 2 to 3, 17.1% 4 to 5, 79.0% 6 or more, high-stimulation; 5.9% 2 to 3, 12.9% 4 to 5, 81.2% 6 or more, medium-stimulation; 5.9% 2 to 3, 9.9% 4 to 5, 84.2% 6 or more, low-stimulation			
Hein et al., 2013[81] Psychiatric hospital, Germany None	To investigate the effects of auricular tVNS in patients with depression RCT 2 weeks	Inclusion criteria (must meet all): diagnosis of MDE Exclusion criteria (excluded if any criteria met): inflammatory, cardiac, endocrine, renal or hepatic disease; alcohol or drug dependence	Total N = 37, comprising 18 in the tVNS group and 19 in the sham group Sex: 61% female, tVNS; 58% female, sham tVNS Mean age (SD): 46.5 years (10.2), tVNS; 46.9 years (11.0), sham tVNS Median duration of current episode (range): 2 months (0 to 12), tVNS; 1.5	• tVNS (once or twice a day)	• Sham tVNS (device was turned off)	• Depression severity • Harms

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
			months (1 to 24), sham tVNS Type of depression: 72% recurrent, 28% single-episode, tVNS; 63% recurrent, 37% single-episode, sham tVNS Mean time since first onset of depression (SD): 8.6 years (11.5), tVNS; 5.3 years (7.7), sham tVNS Median number of antidepressants (range): 1.5 (0 to 4), tVNS; 2 (1 to 3), sham tVNS Calculated from Table 1 in the published paper			
Rush et al., 2005[85] Nierenberg et al., 2008[84] 21 sites in the U.S. NCT00533832	To compare adjunctive VNS with sham treatment in people with nonpsychotic major depressive disorder or	Inclusion criteria (must meet all): primary diagnosis of MDD or bipolar I or II disorder; current MDE of 2 years or more, or had at least 4 lifetime MDEs, including the current MDE; TRD, defined as	Total N = 222, comprising 112 in the VNS group and 110 in the sham VNS group Mean age (SD): 47.0 (9.0), VNS; 45.9 (9.0), sham Median age (range): 47.0 years (24 to 72),	• VNS	• Sham VNS (device was not turned on)	• Depression severity • Mortality • Suicidal ideation and severity • Response and duration of response

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
	nonpsychotic, depressed phase, bipolar disorder RCT 10 weeks of active treatments	having an unsatisfactory response to at least 2 adequate trials of different classes of antidepressant medication, but not more than 6, regardless of antidepressant category in the current MDE; aged 18 to 80 years; use of acceptable birth control methods (including abstinence) in women; mean baseline score of the $HRSD_{24}$ of 20 more; participants with bipolar disorder had to be resistant to, intolerant of, or have a medical contraindication to lithium Exclusion criteria (excluded if any criteria met): pregnancy; atypical or psychotic features in any MDE; lifetime history of any	VNS; 47.0 years (24 to 68), sham Sex: 59% female, VNS; 66% female, sham Race or ethnicity: 97% Caucasian, VNS; 96%, Caucasian, sham Type of depression: 81.3% recurrent MDD, 7.1% single-episode MDD, 5.4% bipolar I, 6.3% bipolar II, VNS; 74.5% recurrent MDD, 6.4% single-episode MDD, 3.6% bipolar I, 5.5% bipolar II, sham Mean duration of current MDE (SD): 46.6 months (51.3), VNS; 51.7 months (52.2), sham Median duration of current MDE (range): 32.5 months (4 to 354), VNS; 34.0 months (3 to 245), sham Mean age at onset of depression (SD); 21.9			• Treatment withdrawal • Quality of life • Harms • Failure rate

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
		nonmood psychotic disorder (e.g., schizophrenia); current rapid cycling bipolar disorder; or a current secondary diagnosis of delirium, dementia, amnesia, or other cognitive disorder; clinically significant current suicidal intent; certain risks related to surgical implantation of VNS	years (11.0), VNS; 22.1 years (12.5), sham Mean duration of depression (SD): 26.1 years (11.0), VNS; 24.9 years (13.0), sham Median duration of depression (range): 26.5 years (4 to 48), VNS; 25.0 years (3 to 57), sham Lifetime number of MDEs: 22% ≤2, 39% 3 to 5, 24% 6 to 10, 8% > 10, 6% unknown, VNS; 26% ≤2, 28% 3 to 5, 29% 6 to 10, 14% > 10, 4% unknown, sham Mean hospitalizations (SD); 2.9 (6.6), VNS; 2.3 (3.6), sham Median hospitalizations (range); 1.0 (0 to 64), VNS; 1.0 (0 to 20), sham			

Citation Setting NCT Number or Study Name	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Intervention	Comparator(s)	Relevant Outcomes Measured
			Receiving ECT in the current MDE: 33.2%, VNS; 38.2%, sham Receiving ECT in lifetime: 51.8%, VNS; 53.6%, sham Mean $HRSD_{24}$ score (SD): 28.8 (5.3), VNS; 29.7 (5.2), sham Mean MADRS score (SD): 31.4 (6.3), VNS; 31.9 (6.3), sham Mean IDS-SR_{30} score (SD): 44.3 (9.1), VNS; 45.4 (8.5), sham *See Table C2 for treatment-resistant status*			

Abbreviations. AED: antiepileptic drug; BMP: best medical practice; CPS: complex partial seizure; DBS: deep brain stimulation; ECT: electroconvulsive therapy; HRSD: Hamilton Rating Scale for Depression; IDS-SR: Inventory of Depressive Symptomatology-Self-Report; ILAE: International League Against Epilepsy; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; MDE: major depressive episode; NCT: U.S. National Clinical Trial; QoL: quality of life; RCT: randomized controlled trial; SD: standard deviation; TRD: treatment-resistant depression; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

Table C2. Treatment-Resistance by Treatment Group at Baseline (Rush et al., 2005)[85]

Number of Unsuccessful Treatments	VNS	Sham VNS
2	30.4%	31.8%
3	23.2%	28.2%
4	20.5%	18.2%
5	17.0%	12.7%
6[a]	9.0%	9.1%

Note. [a] *1 participant in the VNS group failed 7 treatments. Abbreviation. VNS: vagal nerve stimulation.*

Table C3. Evidence Tables for Randomized Controlled Trials

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
Epilepsy				
Bauer et al., 2016[79] 9 sites in Germany and 1 site in Austria cMPsE02	Seizure Frequency Change in mean seizure frequency per 28 days (SD): -23.4% (47.2), high-stimulation; 2.9% (94.4), low-stimulation Least-square mean difference from baseline to end of treatment: -22.9% (95% CI, -47.5% to 1.7%; *P* = .07 from baseline), high-stimulation; 2.4% (95% CI, -21.5% to 26.4%; *P* = .84 from baseline), low-stimulation Least-square mean difference between groups at end of treatment: -25.3% (95% CI, -59.7% to 9.0%); *P* = .15 Mean change in seizure frequency from baseline in 26 patients who	Treatment Withdrawal In the high-stimulation group, 10 of 37 (27%) did not complete the study: • n = 3, no compliance with study requirements • n = 1, withdrawal of consent • n = 1, condition described in the inclusion/exclusion criteria • n = 1, further participation would put the participant at risk • n = 4, other In the low-stimulation group, 8 of 39 (21%) did not complete the study:	Harms See Table C4 for details 4 serious adverse events occurred: • n = 1 palpitations, rated as possibly or probably treatment-related • n = 1 vestibular neuronitis, relationship with treatment unclear • n = 1 suspected basal cell carcinoma that was not confirmed by histology • n = 1 SUDEP death in the low-stimulation group, which was not rated as being related to treatment	No significant differences were seen in subgroup analyses by gender, seizure type, baseline seizure frequency, and concurrent treatment with drugs other than AEDs

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	completed the 20 weeks treatment: -34.2%; *P* = .03 Mean changes in seizures per 28 days: -2 (*P* = .07), high-stimulation; nearly 1 (*P* = .39), low-stimulation Mean changes in seizures per 28 days in 26 patients who completed the 20 weeks treatment: -3 (*P* = .03), high-stimulation; -1.2 (*P* = .34), low-stimulation Response (defined as ≥ 25% reduction in seizures); 48.6%, high-stimulation, 48.7%, low-stimulation (*P* value not reported) Response (defined as ≥ 50% reduction in seizures); 27.0%, high-stimulation, 25.6%, low-stimulation (*P* value not reported) Seizure Freedom Complete response (defined as 100% reduction in seizures); 1 of 39 (2.6%), high-stimulation, 3 of 39 (7.7%), low-stimulation (*P* value not reported) Seizure Severity Mean change in LSSS score: 1.56, high-stimulation (*P* = .08); 0.83, low-stimulation (*P* = .19); *P* > .05 between groups	• n = 1, no compliance with study requirements • n = 1, withdrawal of consent • n = 1, death • n = 5, other Mood or Cognitive Changes Mean change in MADRS score: -1.14, high-stimulation (*P* = .06); -0.93, low-stimulation (*P* = .11); *P* > .05 between groups Quality of Life Mean change in QOLIE-31-P score: 2.68, high-stimulation (*P* = .08); 4.65, low-stimulation (*P* = .01); *P* > .05 between groups CGI-I at end of treatment: 54.0% improved, 35.1% no change, 10.8% worsened, high-stimulation; 48.7% improved, 43.6% no change, 7.7% worsened, low-stimulation; *P* value not reported	Voice alteration and coughing were not observed Reimplantation Not reported Failure Rate Not reported	

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	Seizure Duration Not reported			
Handforth et al., 1998[80] Dodrill et al., 2001[49] 20 sites in the U.S. E05	Seizure Frequency Mean change in seizure frequency (SD): -27.9% (34.3), high-stimulation; -15.2 (39.2), low-stimulation; *P* < .001 from baseline for each group Mean difference between groups: -12.7%; 95% CI, -23.1 to -2.3) Mean change in partial seizure frequency (SD): -26.6% (36.8), high-stimulation; -13.4 (40.1), low-stimulation; *P* < .001 from baseline for each group Mean difference between groups: -13.2%; 95% CI, -24.1 to -2.3) Response (defined as ≥ 50% reduction in seizures); 22 of 94 (23.4%), high-stimulation, 16 of 102 (15.7%), low-stimulation; *P* = .17 Response (defined as ≥ 75% reduction in seizures); 10 of 94 (10.6%), high-stimulation, 2 of 102 (2.0%), low-stimulation; *P* = .02 Seizure Freedom	Treatment Withdrawal In the high-stimulation group, 3 of 95 (3%) did not complete the study: • n = 1, poor compliance • n = 1, adverse event • n = 1, uninterpretable diary In the low-stimulation group, 1 of 103 (< 1%) did not complete the study: • n = 1, withdrawal of consent Mood or Cognitive Changes No differences were seen for cognitive task performance (Wonderlic Personnel Test, Digit Cancellation, Stroop Test, Symbol Digit Modalities) between the 2 groups Quality of Life In both stimulation groups, patient, interviewer, and companion ratings of patient well-being were higher at the end of treatment than at baseline (*P* < .001)	Harms See Table C6 Surgery-related complications: vocal cord paralysis in 2 patients, lower facial muscle paralysis in 2 patients, fluid accumulation in 1 patient All complications resolved Interviewers were more likely to assess a symptom as treatment-related in the high-stimulation group as in the low-stimulation group for voice alteration (47.4% vs. 9.7%), dyspnea (11.6% vs. 1.0%) and pharyngitis (15.8% vs. 3.9%) Paresthesia and cough were more common during treatment than at baseline, but were similar between groups Most symptoms were mild or moderate, well-tolerated, and did not require a reduction in stimulation	In the high-stimulation group, patients without auras had a similar reduction in seizure frequency than patients with auras (a mean of 27.4% vs. 26.8%; *P* value not reported Use of AEDs remained similar before and during treatment

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	In the high-stimulation group, 1 patient became seizure-free during the 3 month study period Assumed that no participants in the low-stimulation group became seizure-free during the 3 month study period (not reported explicitly) Seizure Severity Not reported Seizure Duration Not reported	Mean difference between groups in patient well-being, as rated by the interviewer: 4.0 mm (95% CI, 0.6 to 7.4) Mean difference between groups in patient well-being, as rated by the patient: 6.6 mm (95% CI, 2.2 to 11.0) Companion-rated well-being was similar between groups (reported graphically; $P > .05$) Interviewers rated more high-stimulation patients than low-stimulation patients having well-being of 25 mm or more ($P = .01$) and at 37.5 mm or more ($P = .02$). More high-stimulation patients than low-stimulation patients rated themselves at 37.5 mm or more ($P < 0.05$) but for 25 mm or more, the difference was not significant ($P = 0.08$) See Table C5 for detailed QoL outcomes	Central nervous symptoms were not observed Reimplantation Of the 3 devices removed after infection, 1 was reimplanted during the study Failure Rate Infection, leading to device removal, occurred in 3 patients In the high-stimulation group, 1 patient had postictal Cheynes-Stokes respiration which resolved on deactivation In the low-stimulation group, 1 patient experienced a variety of symptoms before and after implantation, which were judged as being unrelated to treatment No devices malfunctioned	

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
Klinkenberg et al., 2012[82] Klinkenberg et al., 2013[83] University medical center, Netherlands None	<u>Seizure Frequency</u> Response (defined as a 50% reduction or more): 3 of 19 (16%), high-stimulation; 4 of 19 (21%), low-stimulation; *P* = 1.00 (Note. If based on the number randomized, 3 of 21 in the high-stimulation group and 4 of 20 in the low-stimulation group responded) Median change in seizure frequency: 23.4%, high-stimulation; -8.8%, low-stimulation; *P* = .61 Median change in seizure frequency in the last 30 days of blinded treatment: -3.1%, high-stimulation; -5.1%, low-stimulation; *P* = .47 At the end of the 19 weeks add-on phase (all children received high-stimulation), 9 of 34 (26%) experienced a 50% or more seizure frequency reduction, 5 (15%) experienced a 50% or more increase, and 20 (59%) did not respond at all At the end of the 19 weeks add-on phase (all children received high-stimulation), seizure frequency decreased from a	<u>Treatment Withdrawal</u> In the high-stimulation group, 2 of 21 (10%) did not complete the study: • n = 2, unreliable or incomplete diary In the high-stimulation group, 1 of 20 (5%) did not complete the study: • n = 1, unreliable or incomplete diary <u>Mood or Cognitive Changes</u> No differences were seen between the high- and low-stimulation groups for measures of cognition, mood, epilepsy-related restrictions or psychosocial adjustment At the end of the 19 weeks add-on phase (all children received high-stimulation), there was a significant improvement in depression (*P* = .03) from baseline but no significant changes in cognition, total mood disturbance, epilepsy-related restrictions or psychosocial adjustment <u>Quality of Life</u> Not reported	<u>Harms</u> See Table C7 for details The majority were transient and most were stimulus-related Reported behavioral changes consisted of agitation, crying, or frequent startles Wound infection occurred in 2 participants with both infections successfully treated with antibiotics There were no other surgery-related side effects <u>Reimplantation</u> Not reported <u>Failure Rate</u> Not reported	Children with a lower age at onset tended to have a better response (*P* = .08)

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	median of 1.61 seizures per day during the baseline phase to a median of 1.12 seizures per day at the end of the add-on phase (*P* = .02) Seizure Freedom Not reported Seizure Severity Mean change in NHS3 score: -0.3, high-stimulation; -0.6, low-stimulation; *P* = .71 At the end of the 19 weeks add-on phase (all children received high-stimulation), seizure severity decreased from a mean score of 9.5 at baseline to 8.3 at the end of the add-on phase (*P*< .001) Seizure Duration Not reported			
Landy et al., 1993[51] University hospital, U.S. None	Seizure Frequency Mean change in seizure frequency from baseline to a minimum of 12 weeks (SD):-23.31% (18.65), high-stimulation; 12.77% (31.88), low-stimulation; *P* > .05 Note. When these data are input to Review Manager, the result appears to be significant Mean change in seizure frequency from baseline to the end of the open phase (a minimum of 18	Treatment Withdrawal Not reported Mood or Cognitive Changes Not reported Quality of Life Not reported	Harms Not reported for the randomized subgroup Reimplantation Not reported Failure Rate VNS devices remained in place for periods of 6 to 13 months with no further delayed complications	No other relevant outcomes reported

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	weeks) (SD):-36.44% (11.58), high-stimulation; -23.44% (47.75), low-stimulation; *P* value not reported Mean change in seizure frequency from the blinded phase to the end of the open phase (SD):-16.09% (8.26), high-stimulation; -35.59% (38.25), low-stimulation; *P* value not reported Median change in seizure frequency from baseline to a minimum of 12 weeks:-27.73%, high-stimulation; 6.30%, low-stimulation; *P* > .05 Median change in seizure frequency from baseline to the end of the open phase (a minimum of 38 weeks):-36.24%, high-stimulation; -16.32% (47.75), low-stimulation; *P* < .02 for the combined group Median change in seizure frequency from the blinded phase to the end of the open phase: -14.33%, high-stimulation; -25.43%, low-stimulation; *P* value not reported Seizure Freedom Not reported Seizure Severity			

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	Not reported Seizure Duration No comparative data reported			
Ryvlin et al., 2014[86] 28 sites in Europe and Canada NCT00522418,PuLsE	Seizure Frequency The reduction in seizure frequency from baseline to 12 months was significantly greater in the VNS+BMP group compared with the BMP group (*P* = .03) Median percent change in seizure frequency from baseline to 12 months showed increasing improvement in seizure control for the VNS+BMP group vs. the BMP group over time,, although the difference between groups was not significant at any time point (reported graphically) Response (defined as 50% or greater reduction in seizure frequency): 10 of 31 (32%), VNS+BMP; 7 of 29 (24%); *P* = .49 Seizure Freedom Not reported Seizure Severity Not reported Seizure Duration Not reported	Treatment Withdrawal In the VNS+BMP group, 6 participants were excluded from the analysis: • n = 2, premature study termination • n = 1, withdrawal of consent • n = 1, compliance • n = 2, other In the BMP group, 10 participants were excluded from the analysis: • n = 7, premature study termination • n = 1, withdrawal of consent • n = 1, compliance • n = 1, lack of efficacy Discontinuations due to premature termination of the study by the sponsor: 46 of 54, (85%) VNS+BMP; 47 of 58 (81%), BMP No discontinuations due to an adverse event seen in either treatment group. Mood or Cognitive Changes	Harms See Table C8 for the Adverse Event Profile Score In the VNS+BMP group, 23 (43%) patients reported adverse events, with the majority being related to VNS therapy • Device implantation (n = 12; 22%) • Electrode stimulation (n = 11; 20% Other adverse events reported in the VNS+BMP group were dysphonia (15%), chest pain (6%), headache (6%), hypoesthesia (6%), and depression (6%). Of these chest pain and hypoesthesia were considered related to VNS device implantation and dysphonia was considered related to device stimulation. In addition, 1 patient experienced localized infection related to device implantation.	No other relevant outcomes reported

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
		See Table C8 for mood outcomes Quality of Life See Table C8 for QoL outcomes There was no consistent patterns in the time to effect, if significant	In the BMP group, 12 (21%) patients reported adverse events (no details reported) Serious adverse events were reported in 5 (9%) patients in the VNS+BMP group and in 3 (5%) patients in the BMP group. In the VNS + BMP group, serious adverse events included • Transient vocal cord paralysis in 2 patients (considered to be related to the implantation procedure; both completely resolved) • Brief respiratory arrest of moderate severity in 1 patient from postoperative laryngospasm (considered related to implantation procedure and AED treatment; resolved on the same day) • Fall, convulsion, head injury, and worsened seizures in 1 patient (considered related to VNS stimulation and AED treatment)	

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
			• Prostatic cancer in 1 patient (not considered related to study treatment) • Suicide attempt in 1 patient (not considered related to study treatment) None of the serious adverse events in the BMP group were considered related to AED treatment (no details reported) No deaths were observed in either group Reimplantation Not reported Failure Rate Not reported	
Vagus Nerve Stimulation Group, 1995[87] Elger et al., 2000[50] 17 sites in the U.S., Canada, and Europe E03	Seizure Frequency More patients in the high-stimulation group experienced a decrease in seizure frequency (reported graphically) Mean change in seizure frequency: -24.5% (95% CI, -34.9% to -14.1%; *P* < .01 from baseline), high-stimulation; -6.1% (95% CI, -15.8% to 3.6%; *P* = .21 from baseline), low-stimulation; *P* = .01 between groups	Treatment Withdrawal See Harms Not reported by group Mood or Cognitive Changes In 11 participants with > 4 medication-resistant complex-partial seizures per month, significant positive mood effects were observed in most scales and	Harms See Table C9 for harms In the high-stimulation group, 1 patient experienced a nonfatal myocardial infarction, resulting in the generator being deactivated and the device removed Reimplantation Not reported Failure Rate	In an analysis limited to patients with 6 or more CPSs and SGSs per month, the mean change in seizure frequency: -24.0%, high-stimulation; -12.5%, low-stimulation; *P* = .08 In an analysis limited to patients with 6 or

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	Mean change in seizure frequency (if 24 patients with major protocol violations were excluded): -27.9%, high-stimulation; -6.31%, low-stimulation; *P* < .01 Median change in seizures per day: 0.73 to 0.42 (*P*< .01 from baseline), high-stimulation; 0.82 to 0.82 (*P* = .19 from baseline), low-stimulation; *P* = .02 between groups Reduction of ≥ 50% in seizure frequency: 31%, high-stimulation; 13%, low-stimulation; *P* = .02 Reduction of ≥ 50% in seizure frequency (if 24 patients with major protocol violations were excluded): 35%, high-stimulation; 15%, low-stimulation; *P* < .05 In the high-stimulation group, 4 patients had a 75% or more reduction in seizure frequency compared with 1 patient in the low-stimulation group (*P* value not reported) Seizure Freedom No patients in either group became seizure free Seizure Severity Not reported	subscales at 3 months (*P*< .05) Mood improvements were sustained at 6 months in 11 participants with > 4 medication-resistant complex-partial seizures per month and improvements were independent of effects on seizure activity (9 of 11 mood responders versus 2 of 11 seizure responders) Quality of Life Not reported	2 signal generators malfunctioned, resulting in 1 case of ongoing vocal cord paralysis There were no cases of intrinsic wire lead or electrode failure Reoperation was required in 1 case of lead detachment	more CPSs and SGSs per month, the mean change in seizure frequency (if 24 patients with major protocol violations were excluded): -25.8%, high-stimulation; -11.8%, low-stimulation; *P* value not reported In the high-stimulation group, there was no significant differences in seizure frequency by type of partial seizure.

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	Seizure Duration Not reported			
Depression				
Aaronson et al., 2013[78] 29 academic and clinical sites in the U.S. NCT00305565, D-21	Depression Severity At week 22, no significant differences were seen between the treatment groups for the change in mean IDS-C score over time (*P* = .81, low vs. medium-stimulation; *P* = .80, low vs. high-stimulation; *P* = .99, medium vs. high-stimulation) At week 22, mean IDS-C scores showed statistically significant improvement during the weeks after the initiation of stimulation for all treatment groups combined (*P* = .002) At week 22, there was a statistically significant improvement observed for all treatment groups combined: *P* < .001 for QIDS-C, *P* < .001 for MADRS, *P* < .001 for CGI-I, and *P* < .001 for IDS-SR, but there was no significant differences between treatment groups At week 50, depression symptoms, as measured by IDS-C scores, continued to improve but there were no differences	Treatment Withdrawal Withdrawals: 2 of 107 (1.9%) high-stimulation; 4 of 101 (4.0%) medium-stimulation; 5 of 102 (4.9%) low-stimulation Compliance with Other Depression Treatment Not reported Cognitive Changes Not reported Quality of Life Not reported Sleep Not reported	Harms See Tables C11 and C12 for details Serious adverse events were reported in 66 of 331 patients (19.9%) Most serious adverse events were reported in 1 to 3 patients in all 3 dose groups combined (i.e., reported in less than 1% of total patients per serious adverse events), except for: • Suicide attempts were more frequent in the low-stimulation group (6.3%) than in the medium-stimulation (0.9%) or the high-stimulation groups (3.5%) (low vs. combined medium and high groups, *P* = .07) • Depression was more frequent in the low-stimulation group (7.2%) compared with the medium-stimulation (5.6%) or high-	No other relevant outcomes reported

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	between groups (reported graphically) Mortality 6 patients died • 1 patient died from a pulmonary embolism following bariatric surgery • 1 patient died in a motor vehicle accident • 2 patients died from cardiovascular system related causes (both had pre-existing cardiovascular disease) • 2 patients died of suicide (1 patient in the low-stimulation group with a history of 2 lifetime suicide attempts and 1 patient in the high-stimulation group with no history of prior suicide attempts, but the investigator considered the event to be not related to VNS implantation or stimulation) See Harms Suicidal Ideation and Severity See Harms Response and Duration of Response At week 22, response (defined as at least a 50% improvement in symptoms) was not significantly		stimulation (3.5%) groups Reimplantation Not reported Failure Rate Not reported	

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	different between treatment groups (reported graphically) At week 50, response was numerically higher than at week 22, but there was no difference between treatment groups (reported graphically) See Table C10 for sustained response rates Sustained response (the number of responders at week 22 who continued to response at week 50) in the high and medium-stimulation groups was higher than in the low-stimulation group on both the IDS-C (81.8%, high-stimulation; 88.2%, medium-stimulation; 43.8%, low-stimulation; low vs. medium, *P* = .02; low vs. high, *P* = .02) but not the MADRS (76.7%, high-stimulation; 92.0%, medium-stimulation; 68.8%, low-stimulation; *P* > .05) <u>Remission and Duration of Remission</u> At week 22, remission (defined as score of ≤ 14 on the IDS-C and IDS-SR, ≤ 5 on the QIDS-C, or ≤ 9 on the MADRS) was not significantly different between			

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	treatment groups (reported graphically; 5% to 6% low; 9% to 11% in the medium and high groups) At week 50, response was numerically higher than at week 22, but there was no difference between treatment groups (reported graphically) Anxiety See Harms			
Hein et al., 2013[81] Psychiatric hospital, Germany None	Depression Severity Mean change in HAM-D from baseline (SD): -5.4 (5.7), tVNS; -6.6 (7.1), sham tVNS; *P* > .05 Mean change in BDI from baseline (SD): -12.6 (6.0), tVNS; -4.4 (9.9), sham tVNS; *P* < .05 Mortality Not reported Suicidal Ideation and Severity Not reported Response and Duration of Response Not reported Remission and Duration of Remission Not reported Anxiety Not reported	Treatment Withdrawal Not reported Compliance with Other Depression Treatment Not reported Cognitive Changes Not reported Quality of Life Not reported Sleep Not reported	Harms No unpleasant sensations during or after the stimulation procedures were reported No local skin irritations or unpleasant acoustic or vestibular reactions were observed No adverse side effects were observed or reported after the trial Reimplantation Not reported Failure Rate Not reported	No other relevant outcomes reported

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
Rush et al., 2005[85] Nierenberg et al., 2008[84] 21 sites in the U.S. NCT00533832	Depression Severity Mean improvement from baseline (SD), $HRSD_{24}$: 16.3% (28.1), VNS; 15.3% (25.5), sham; *P* = .64 Mean improvement from baseline (SD), MADRS: 17.1% (31.21), VNS; 12.4% (27.1), sham; *P* = .21 Mean improvement from baseline (SD), $IDS\text{-}SR_{30}$: 21.2% (25.4), VNS; 16.3% (26.2), sham; *P* = .16 Estimated difference between groups, $HRSD_{24}$: -0.77 (95% CI, -2.34 to 0.80) Estimated difference between groups, $IDS\text{-}SR_{30}$: -2.37 (95% CI, -4.78 to 0.03) Mortality In the VNS group, 1 participant died of suicide after 5 weeks of treatment, which was assessed as being condition-related and not treatment-related Suicidal Ideation and Severity See Mortality Response and Duration of Response Response rate, defined as ≥ 50% reduction from baseline on the $HRSD_{24}$ score: 15.2%, VNS; 10.0%, sham; *P* = .25	Treatment Withdrawal See Harms Compliance with Other Depression Treatment Not reported Cognitive Changes Not reported Quality of Life Mean change in the physical component of the SF-36 (SD): -0.9 (8.3), VNS; -1.6 (8.4), sham; *P* = .48 Mean change in the mental component of the SF-36 (SD): 5.0 (11.6), VNS; 4.0 (10.2), sham; *P* = .41 Sleep Not reported	Harms 3 participants in the VNS group withdrew because of adverse events, including 1 suicide 1 device was removed because of infection 27 participants experienced 30 serious adverse events (16, VNS; 14, sham) • 12 episodes of hospitalization for worsening depression (4 participants, VNS; 7 participants, sham; 1 participant, VNS but who had not yet received stimulation) • 1 case of asystole during surgery in the VNS group • 1 case of bradycardia during surgery in the VNS group • 2 participants in the VNS group exhibited significant hypomania or mania, which resolved spontaneously after 1 to 2 weeks Reimplantation Not reported	In the VNS group, there were no significant differences for quality of life (mental or physical components) in people with between unipolar or bipolar depression over 12 months of treatment In the VNS group, there were no significant differences in response in people with between unipolar or bipolar depression over 24 months of treatment OR of response in unipolar patients compared with bipolar patients at 24 months, $HRSD_{24}$: 0.95 (95% CI, 0.46 to 1.95) OR of response in unipolar patients compared with bipolar patients at

Citation Setting NCT Number or Study Name	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	Response rate, defined as ≥ 50% reduction from baseline on the MADRS score: 15.2%, VNS; 11.0%, sham; *P* = .38 Response rate, defined as CGI-I score of 1 or 2 (much or very much improved): 13.9%, VNS; 11.8%, sham; *P* = .65 Response rate, defined as ≥ 50% reduction from baseline on the IDS-SR_{30} score: 17.0%, VNS; 7.3%, sham; *P* = .03 Remission and Duration of Remission Not reported Anxiety Not reported		Failure Rate Not reported	24 months, IDS-SR_{30}: 0.49 (95% CI, 0.22 to 1.09) Mean proportion of visits with response (SD), $HRSD_{24}$: .24 (0.29), unipolar; .24 (0.28), bipolar; *P* = .73 Mean proportion of visits with response (SD), IDS-SR_{30}: .18 (0.28), unipolar; .29 (0.35), bipolar; *P* = .21

Abbreviations. AED: antiepileptic drug; BDI: Beck Depression Inventory; BMP: best medical practice; CGI-I: Clinical Global Impression – Improvement scale; CI: confidence interval; CPS: complex partial seizure; HAM-D; Hamilton Depression Rating Scale; HRSD: Hamilton Rating Scale for Depression; IDS-C: Inventory of Depressive Symptomatology - Clinician version; IDS-SR: Inventory of Depressive Symptomatology - Self-Report version; LSSS: Liverpool Seizure Severity Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; NCT: U.S. National Clinical Trial; NHS3: Chalfont Seizure Severity Scale; OR: odds ratio; QIDS-C: Quick Inventory of Depressive Symptoms - Clinician version; QoL: quality of life; QOLIE-31-P: Quality of Life in Epilepsy–31-P; SD: standard deviation; SF-36: Short-Form Health Survey-36; SGS; secondary generalized seizure; SUDEP: sudden unexpected death in epilepsy; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

Table C4. Most Frequent Adverse Events (Bauer et al., 2016[79])

Adverse Event	High-stimulation Group			Low-stimulation Group		
	Events	Participants	%	Events	Participants	%
Headache	30	12	32.4%	24	14	35.9%
Nasopharyngitis	13	10	27.0%	12	8	20.5%
Ear Pain	8	6	16.2%	5	3	7.7%
Dizziness	11	5	13.5%	2	2	5.1%
Vertigo	7	4	10.8%	6	3	7.7%
Nausea	8	3	8.1%	7	3	7.7%
Fatigue	2	1	2.7%	5	5	12.8%
Diarrhoea	2	2	5.4%	5	3	7.7%
Application Site Erythema	3	3	8.1%	1	1	2.6%

Table C5. Quality of Life Outcomes by Treatment Group (Handforth et al., 1998[49,80])

Outcome	High-stimulation N = 78		Low-stimulation N = 82		P Value Group x Time Interaction
	Baseline Mean (SD)	Treatment Mean (SD)	Baseline Mean (SD)	Treatment Mean (SD)	
SF-36: Role Physical	68.51 (34.32)	76.17 (27.23)	62.18 (33.04)	64.00 (33.20)	*P* = .04
SF-36: Role Emotional	76.09 (27.36)	85.87 (21.51)	72.73 (32.01)	74.09 (33.32)	*P* = .03
Washington Psychosocial Seizure Inventory: Financial Status	2.60 (2.22)	2.25 (2.06)	2.89 (2.11)	2.91 (2.07)	*P* = .03

Note. All other subscales of the SF-36 and the Washington Psychosocial Seizure Inventory were not significantly different between groups. Other features of quality of life measured using the Quality of Life in Epilepsy-31, Medical Outcomes Study, and Health-Related Hardiness Scale tools were also not significantly different between groups. Abbreviations.SD: standard deviation; SF: Short-Form Health Survey.

Table C6. Adverse Events Occurring in > 10% of High-stimulation Participants (Handforth et al., 1998[80])

Adverse Event	High-stimulation N = 95	Low-stimulation N = 103	P Value
Voice Alteration	63 (66.3%)	31 (30.1%)	*P* = .001
Cough	43 (45.3%)	44 (42.7%)	*P* < .001
Pharyngitis	33 (34.7%)	26 (25.2%)	*P* > .05
Pain	27 (28.4%)	31 (30.1%)	*P* > .05
Dyspnea	24 (25.3%)	11 (10.7%)	*P* = .007
Headache	23 (24.2%)	24 (23.3%)	*P* > .05
Dyspepsia	17 (17.9%)	13 (12.6%)	*P* > .05
Vomiting	17 (17.9%)	14 (13.6%)	*P* > .05
Paresthesia	17 (17.9%)	26 (25.2%)	*P* < .001
Nausea	14 (14.7%)	21 (20.4%)	*P* > .05
Accidental Injury	12 (12.6%)	13 (12.6%)	*P* > .05
Fever	11 (11.6%)	19 (18.4%)	*P* > .05
Infection	11 (11.6%)	12 (11.7%)	*P* > .05

Table C7. Adverse Events Reported by Children, Parents, or Guardians (Klinkenberg et al., 2012[82])

Adverse Event	Number of Participants
Voice Alterations	8
Coughing	3
Throat Pain	3
Tingling Sensations in Throat	2
Behavioral Changes	3
Infection	2
Headache	1
Spontaneous Swelling Around Stimulator	1
Pain Around Stimulator During Exercise	1
Itch	1

Table C8. Depression, Health-related Quality of Life and Adverse Event Outcomes by Treatment Group (Ryvlin et al., 2014[86])

Outcome	VNS+BMP	BMP	P Value
QOLIE-89 Score			
Baseline Mean (SD)	43.1 (10.1)	44.8 (9.9)	*P* = .19
Mean Change (SD) From Baseline to 12 Months	5.5 (7.2)	1.2 (6.9)	*P* = .01
3.1 (0.9)	0.6 (0.9)	*P* < .05	3.1 (0.9)
CGI-I Score			
Baseline Mean (SD)	4.1 (0.4)	4.0 (0.5)	*P* = .40
Mean Change (SD) From Baseline to 12 Months	-0.8 (0.8)	-0.3 (1.1)	*P* = .03
MMRM LS Mean (SE)	-0.6 (0.1)	-0.2 (0.1)	*P* = .01
CES-D Score			
Baseline Mean (SD)	17.1 (9.0)	16.9 (9.5)	*P* = .89
Mean Change (SD) From Baseline to 12 Months	-2.2 (7.0)	0.5 (8.1)	*P* = .17
MMRM LS Mean (SE)	-0.3 (1.0)	-0.5 (1.0)	*P* = .90
NDDI-E Score			
Baseline Mean (SD)	12.5 (4.5)	11.9 (4.2)	*P* = .48
Mean Change (SD) From Baseline to 12 Months	-1.0 (2.2)	-0.2 (3.4)	*P* = .28
MMRM LS Mean (SE)	-0.7 (0.4)	0.1 (0.3)	*P* = .13
AEP Score			
Baseline Mean (SD)	43.1 (10.6)	42.8 (10.6)	*P* = .87
Mean Change (SD) From Baseline to 12 Months	-6.0 (11.4)	-3.2 (6.9)	*P* = .26
MMRM LS Mean (SE)	-3.7 (1.0)	-1.3 (1.0)	*P* = .08

Abbreviations. AEP: Adverse Event Profile; BMP: best medical practice; CES-D: Centre for Epidemiologic Studies Depression; CGI-I: Clinical Global Impression – Improvement; LS: least-square; MMRM: mixed model repeated measures; NDDI-E: Neurological Disorders Depression Inventory-Epilepsy; QOLIE-89: Quality of Life in Epilepsy Inventory-89: SD: standard deviation; SE: standard error; VNS: vagal nerve stimulation.

Table C9. Adverse Events Occurring in at Least 5% of Participants (Vagus Nerve Stimulation Group, 1995[87])

Adverse Event	High-stimulation Group	Low-stimulation Group	P Value
Hoarseness/Voice Change During the Stimulation Burst	37.2%	13.3%	*P* < .01
Throat Pain During the Stimulation Burst	11.1%	11.7%	*P* = 1.00
Coughing During the Stimulation Burst	7.4%	8.3%	*P* = 1.00
Dyspnea During the Stimulation Burst	5.6%	1.7%	*P* = .34
Paresthesia During the Stimulation Burst	5.6%	3.3%	*P* = .67
Muscle Pain During the Stimulation Burst	5.6%	1.7%	*P* = .34
Headache	1.8%	8.3%	*P* = .21

Table C10. Sustained Response by Treatment Group (Aaronson et al., 2013[78])

Outcome	High-stimulation Group N = 113	Medium-stimulation Group N = 107	Low-stimulation Group N = 111	Total N = 331
IDS-C Score				
At Least 50% Improvement at Week 22	22	17	16	55
At Least 50% Improvement at Week 50	18	15	7	40
Responder at Week 22 With Sustained Response at Week 50	81.8%	88.2%	43.8%	72.7%
MADRS Score				
At Least 50% Improvement at Week 22	30	25	16	71
At Least 50% Improvement at Week 50	23	23	11	57
Responder at Week 22 With Sustained Response at Week 50	76.7%	92.0%	68.8%	80.3%

Abbreviations. IDS-C: Inventory of Depressive Symptomatology-Clinician Administered; MADRS: Montgomery-Åsberg Depression Rating Scale.

Table C11. Implantation-related Adverse Events (1% Incidence or Higher) by Treatment Group (Aaronson et al., 2013[78])

Adverse Events	High-stimulation Group N = 113	Medium-stimulation Group N = 107	Low-stimulation Group N = 111	Total N = 331
Incision Pain	16.8%	21.5%	18.0%	18.7%
Incision Site Reaction	8.8%	5.6%	13.5%	9.4%
Voice Alteration	4.4%	12.1%	6.3%	7.6%
Pain	8.8%	4.7%	4.5%	6.0%
Device Site Reaction	2.7%	2.8%	4.5%	3.3%
Paresthesia	3.5%	1.9%	1.8%	2.4%
Pharyngitis	1.8%	1.9%	1.8%	1.8%
Neck Pain	3.5%	0	0.9%	1.5%
Device Site Pain	0	0	3.6%	1.2%

Table C12. Post-implantation Adverse Events (10% Incidence or Higher) by Treatment Group (Aaronson et al., 2013[78])

Adverse Events	High-stimulation Group N = 113	Medium-stimulation Group N = 107	Low-stimulation Group N = 111	Total N = 331
Voice Alteration	76.1%	76.6%	64.0%	72.2%
Dyspnea	33.6%	33.6%	29.7%	32.3%
Pain	41.6%	28.0%	25.2%	31.7%
Paresthesia	34.5%	32.7%	27.9%	31.7%
Incision Pain	23.9%	30.8%	21.6%	24.5%
Increased Cough	24.8%	26.2%	24.3%	25.1%
Headache	18.6%	19.6%	17.1%	18.4%
Depression	18.6%	13.1%	22.5%	18.1%
Pharyngitis	16.8%	17.8%	17.1%	17.2%
Hypertonia	15.0%	15.9%	19.8%	16.9%
Neck Pain	17.7%	13.1%	10.8%	13.9%
Dysphagia	15.9%	15.9%	9.0%	13.6%
Nasopharyngitis	10.6%	15.9%	14.4%	13.6%
Incision Site Reaction	11.5%	10.3%	16.2%	12.7%
Nausea	8.0%	14.0%	13.5%	11.8%
Anxiety	11.5%	11.2%	11.7%	11.5%
Insomnia	10.6%	11.2%	10.8%	10.9%
Device Site Reaction	8.0%	7.5%	14.4%	10.0%

Table C13. Study Characteristics for Nonrandomized and Registry-based Studies

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
Epilepsy					
Amar et al., 2004[57] National registry, U.S. None	To determine the effectiveness of VNS in patients with persistent or recurrent seizures after surgery for intractable epilepsy Subgroup analysis of registry data 24 months	Inclusion criteria (must meet all): included in the registry Exclusion criteria (excluded if any criteria met): undergoing cranial surgery for reasons other than epilepsy were excluded from the prior surgical group	Total N = 4,743, comprising 921 in the prior cranial surgery group and 3,822 in the no prior cranial surgery group Sex: 44.7%, prior cranial surgery; 48.5% female, no prior cranial surgery Median age (range): 28 years (1 to 66) prior cranial surgery; 26 years (0 to 79) no prior cranial surgery Median age at onset (range): 5 years (0 to 62) prior cranial surgery; 4 years (0 to 77) no prior cranial surgery Median duration of epilepsy (range): 19 years (0 to 56) prior cranial surgery; 15.7 years (0 to 66.5) no prior cranial surgery Median seizures per day (range): 1.0 (0 to 242.5) prior cranial surgery; 0.9 (0 to 1,559.0) no prior cranial surgery Seizure type: 75.2% localized, 22.1% generalized, 2.7% other, prior cranial	• VNS with prior cranial surgery	• VNS with no prior cranial surgery

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			surgery; 57.0% localized, 39.5% generalized, 3.4% other, no prior cranial surgery Number of AEDs: 0.4% 0, 10.8% 1, 40.3% 2, 34.9% 3, 10.9% 4, 2.8% ≥ 5, prior cranial surgery; 0.8% 0, 12.8% 1, 41.1% 2, 34.9% 3, 8.7% 4, 1.7% ≥ 5, no prior cranial surgery		
Boon et al., 2002[58] University hospital, Belgium None	To compare epilepsy-related direct medical costs incurred by continued polytherapy with or without novel AEDs, epilepsy surgery, or VNS Nonrandomized, comparative, and prospective Varied, up to 54 months	Inclusion criteria (must meet all): presurgical candidates undergoing presurgical evaluation Exclusion criteria (excluded if any criteria met): none reported	Total N = 84, comprising 25 in the VNS group. 35 in the epilepsy surgical group, and 24 in the continued AED polytherapy group Mean age (range): 31 years (12 to 49), VNS; 32 years (10 to 60), surgery; 34 years (5 to 71), continued AEDs; Mean duration of epilepsy (range): 18 years (4 to 35), VNS; 21 years (4 to 38), surgery; 22 years (2 to 50), continued AEDs; Mean follow-up (range): 29 months (12 to 57), VNS; 28 months (12 to 54), surgery; 25 months (12 to 48), continued AEDs;	• VNS	• Continued polytherapy with AEDs • Epilepsy surgery

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
Ellens et al., 2018[60] Not clear, U.S. None	To compare VNS and RNS efficacy at reducing seizure frequency and complication rates in people with medically intractable epilepsy secondary to CPSs Nonrandomized, comparative, and retrospective Varied, with mean follow-up of 19.5 years	Inclusion criteria (must meet all): diagnosis of medically intractable focal epilepsy Exclusion criteria (excluded if any criteria met): none reported	Total N = 30, comprising 13 in the VNS group and 17 in the RNS group Sex: 6 of 13 (46.2%), VNS; 10 of 17 (58.8%), RNS Mean age (SD): 27.6 years (13.5), VNS; 35.4 years (11.3), RNS 1 participant in each group was aged under 18 Mean duration of epilepsy (SD): 20.7 years (11.1), VNS; 26.5 years (11.8), RNS Mean length of follow-up (SD): 23.1 years (9.7), VNS; 16.8 years (9.7), RNS Median number of seizures per month prior to treatment (IQR): 7.5 (25), VNS; 10 (103), RNS	• VNS	• RNS
Gonen et al., 2015[63] Medical center, Israel None	To compare the outcomes and characteristics of the patients who continued on medical therapy alone with those who underwent VNS implantation in addition to medical therapy Nonrandomized, comparative, and both	Inclusion criteria (must meet all): aged 18 and older; inappropriate for resective epilepsy surgery; pharmacoresistent (defined as the failure to achieve seizure control despite the trial of at least 2 appropriate AEDs with adequate dosage)	Total N = 87, comprising 35 in the VNS group and 52 in the AED group Sex: 42.4% female, VNS; 55.3% female, AED Note. We have assumed the data are mean and SD, but this was not explicitly stated in the paper.	• VNS	• Continued AED treatment

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
	retrospective (baseline) and prospective (follow-up) Minimum follow-up of 12 months	seizures with a deleterious effect on QoL, as reported by patients; elected for less invasive surgery (VNS); at least 1 year of follow-up Exclusion criteria (excluded if any criteria met): prior epilepsy surgery	Mean age (SD): 33.71 years (9.04), VNS; 36.35 years (12.06), AED Mean age at onset of epilepsy (SD): 11.67 years (9.15), VNS; 13.66 years (10.96), AED Mean duration of follow-up (SD): 5.67 years (2.75), VNS; 4.04 years (2.09), AED Mean seizure frequency (SD): 3.52 (0.67), VNS; 3.15 (0.72), AED Mean number of AEDs (SD): 2.91 (0.95), VNS; 2.32 (0.98), AED Family history of epilepsy: 7 of 33 (22.6%), VNS; 7 of 47 (15.2%), AED Febrile seizures: 7 of 33 (22.6%), VNS; 10 of 47 (21.7%), AED Head trauma: 4 of 33 (13.3%), VNS; 10 of 47 (22.2%), AED Status epilepticus: 13 of 33 (41.9%), VNS; 14 of 47 (29.8%), AED		

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			Learning disabilities: 13 of 33 (39.4%), VNS; 5 of 47 (10.6%), AED Cerebral palsy: 6 of 33 (19.4%), VNS; 4 of 47 (8.5%), AED Note. Data as reported in the paper, with some proportions appearing with different percentages		
Harden et al., 2000[64] University hospital, U.S. None	To determine if there was a quantifiable effect on mood of the VNS when used as an antiseizure treatment Nonrandomized, comparative, and prospective Approx. 12 weeks	Inclusion criteria (must meet all): having VNS clinically indicated for seizure control (VNS group), continued seizures but unwilling to change their antiseizure treatment and on a stable AED regimen Exclusion criteria (excluded if any criteria met): progressive structural neurologic illness	Total N = 40, comprising 20 in the VNS group and 20 in the AED group Sex: 70% female, VNS; 70% female, AED Mean age (range): 39.0 years (20 to 58), VNS; 40.2 years (24 to 69), AED Mean seizures per month (SD): 16.2 (19.4), VNS; 3.2 (7.4), AED Seizure type: 12 (60%) CPSs, 5 (25%) CPS with secondary GTC, 3 (15%) primary GTC, VNS; 10 (50%) CPSs, 5 (25%) CPS with secondary GTC, 5 (25%) primary GTC, AED Currently taking antidepressants: 2 (10%), VNS; 0 AED	• VNS	• Continued stable AED treatment

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
Helmers et al., 2003[65] National registry, U.S. None	To compare changes in seizure frequency in 2 groups of patients with pharmacoresistent seizures: the early treatment group, who began VNS therapy 6 years or less after the onset of seizures, and the late treatment group, who began VNS therapy more than 6 years after the onset of seizures Subgroup analysis of registry data 12 months	Inclusion criteria (must meet all): patients registered in the outcome registry Exclusion criteria (excluded if any criteria met): none reported	Total N = 405 participants, comprising 51 with seizures for 6 years or less (early treatment) and 354 with seizures for more than 6 years (late treatment group) Median age at onset (range): 7 years (0 to 53), early treatment; 4.5 years (0 to 47), late treatment Median time between onset of epilepsy and implantation (range): 5 years (1 to 6), early treatment; 19 years (6.5 to 63), late treatment Median age at implantation (range): 12 years (2 to 58), early treatment; 29 years (7 to 71), late treatment Prior cranial surgery: 9 (17.6%), early treatment; 115 (32.5%), late treatment Developmental delay: 14 (27.5%), early treatment; 39 (11.0%), late treatment Median number of seizures per month (range): 33 (0 to 1,801), early treatment; 25 (0 to 6,000), late treatment	• Early VNS treatment	• Late VNS treatment

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			Mean number of AEDs (SD): 2.0 (0.9), early treatment; 2.5 (0.9), late treatment		
Hoppe et al., 2013[66] Not clear, Germany None	To evaluate the therapeutic long-term (> 2 years) effects of adding VNS to best available drug therapy in adults with epilepsy Nonrandomized, comparative, and retrospective (case-control) Mean follow-up of 6.8 years	Inclusion criteria (must meet all): adults who underwent presurgical assessment Exclusion criteria (excluded if any criteria met): prior epilepsy surgery	Total N = 40, comprising 20 in the VNS group and 20 in the drug group Sex: 8 of 20 (40%), female, VNS; 8 of 20 (40%), female, AED Note. We have assumed the data are mean and SD, but this was not explicitly stated in the paper. Mean age (SD): 39.8 years (10.2), VNS; 39.0 years (8.5), AED Mean follow-up (SD): 6.7 years (2.4), VNS; 7.0 years (1.7), AED Mean age at epilepsy onset (SD): 14.1 years (8.8), VNS; 18.1 years (12.2), AED Mean duration of epilepsy (SD): 25.7 years (13.4), VNS; 21.0 years (9.2), AED Etiology: 7 (35%) cryptogenic, 12 (60%) symptomatic, 1 (5%) unclear, VNS; 5 (25%) cryptogenic,	• VNS	• Best available drug treatment (after a failed presurgical evaluation)

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			15 (75%) symptomatic, 0 unclear, AED MRI lesion present: 12 (60%), VNS; 16 (80%), AED Epilepsy syndrome: 8 (40%) focal, 11 (55%) multifocal, 1 (5%) unclear, VNS; 12 (60%) focal, 3 (15%) multifocal, 5 (25%) unclear, AED Number of AEDs: 1 (5%) 1, 9 (45%) 2, 9 (45%) 3, 1 (5%) 4, VNS; 6 (30%) 1, 12 (60%) 2, 2 (10%) 3, 0 4, AED Mean number of AEDs (SD): 2.50 (0.69), VNS; 1.80 (0.62), AED Mean number of SPSs per month (SD): 59.5 (201.6), VNS; 2.8 (7.5), AED Mean number of CPSs per month (SD): 7.9 (8.8), VNS; 5.0 (8.6), AED Mean number of SGSs per month (SD): 1.0 (2.4), VNS; 0.5 (1.2), AED Mean number of seizures per month (SD): 68.4 (206.3), VNS; 8.2 (10.4), AED		

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
Jamy et al., 2019[67] Neuromodulation clinic, U.S. None	To report the practice trends and outcomes accomplished over a year in a highly specialized clinic Nonrandomized, comparative, and retrospective Varied, > 8 months	Inclusion criteria (must meet all): patients with drug-resistant epilepsy undergoing VNS or RNS Exclusion criteria (excluded if any criteria met): none reported	Total N = 43, comprising 27 in the VNS group and 16 in the RNS group Sex: 10 of 27 (37%) female, VNS; 7 of 16 (44%) female, RNS Mean age (range): 34.2 years (19 to 60), VNS; 38.8 years (28 to 58), RNS Epilepsy: 7 of 27 (26%) generalized, 20 of 27 (74%) focal/multifocal, VNS; 5 of 16 (31%) bimedial temporal, 8 of 16 (50%) dominant temporal, 3 of 16 (19%) eloquent cortex, RNS Mean number of AEDs (range): 3.1 (2 to 6) at baseline, 3.2 (2 to 6) at last follow-up, VNS; 3.3 (2 to 5) at baseline, 3.3 (2 to 5) at last follow-up, RNS Previous respective surgery: 3 of 27 (11%), VNS; 6 of 16 (37%), RNS Median age of VNS implant (range): 19 years (11 to 36) Median duration of VNS implant (range): 6 years (1.5 to 24)	• VNS	• RNS

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			Mean duration of epilepsy prior to RNS implantation (range): 24.4 years (range 12 to 39)		
Kawai et al., 2017[68] National registry, Japan None	To evaluate the long-term efficacy of VNS therapy for patients with drug-resistant epilepsy Retrospective analysis of registry data 3 years	Inclusion criteria (must meet all): adults and children; diagnosis of drug-resistant epilepsy; VNS as an adjunctive treatment Exclusion criteria (excluded if any criteria met): people in whom satisfactory outcome would be expected after resective epilepsy surgery	Total N = 385, of whom 23 were excluded from the efficacy analysis • 15 (4%) were undergoing an exchange of an existing implant • 5 (1%) dropped out before the 3-month follow-up • 2 (< 1%) in whom surgery was aborted • 1 (< 1%) did not start stimulation as they became seizure-free Sex: 40.6% female Mean age at seizure onset (SD): 9.1 years (11.6) 69 (19.1%) were aged between 12 and 19 years, with 78 (21.5%) aged under 12 Mean duration of epilepsy (SD): 15.6 years (11.1) Mean age at implantation (SD): 24.8 years (14.7) Mean seizure frequency (SD): 106.0 per week (762.7)	• VNS	• No comparator

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			Mean number of AEDs at registration (SD): 3.4 (1.1) Mean number of AEDs prior to implantation (SD): 5.7 (3.2) Mean duration of AED treatment (SD): 14.7 years (10.6) Prior cranial surgery: 49.7% Resection: 26.8% CC: 227% Seizure type: 24.3% SPS, 50.3% CPS, 47.0% GTC, 5.2% absence, 18.0% tonic, 7.5% myoclonic, 9.4%, atonic, 11.3% spasms Epilepsy classification: 65.7% structural-metabolic, 28.7% unknown, 5.5% genetic		
Kuba et al., 2013[69] University medical center, Czechia None	To compare the effects of resective surgery and VNS on seizure frequency in patients with nonlesional extratemporal epilepsy Nonrandomized, comparative, and retrospective 5 years	Inclusion criteria (must meet all): adults with a diagnosis of nonlesional extratemporal epilepsy Exclusion criteria (excluded if any criteria met): none reported	Total N = 61, comprising 35 in the VNS group and 26 in the surgery group Sex: 18 of 35 (51%) female, VNS; 9 of 26 (35%) female, surgery Note. We have assumed the data are mean and SD, but this was not explicitly stated in the paper.	• VNS	• Surgery

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			Mean age (SD): 32.9 years (8.2), VNS; 27.4 years (8.2), surgery Mean duration of epilepsy (SD): 19.6 years (6.9), VNS; 18.4 years (6.1%), surgery In the VNS group, 18 of 35 patients (51.3%) had frontal lobe epilepsy, 13 of 35 (37.1%) were not able to have the seizure onset zone location located, and 1 patient each (2.9%) of parietal lobe epilepsy, pericentral region epilepsy, opercular insular epilepsy, and multifocal epilepsy In the surgery group, 14 of 26 (53.8%) patients had seizure onset zone location in the frontal lobe, 5 of 26 (19.2%) patients in the parietal lobe (PLE), 4 of 26 (15.4%) patients in the pericentral region, and 3 of 26 (11.6%) patients in the occipital lobe Invasive EEG: 5 of 35 (14.3%), VNS; 26 of 26 (100%), surgery		

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			Prior stereotactic partial callosotomy: 6 of 35 (17.2%), VNS; 0, surgery History of unsuccessful respective surgery: 3 of 35 (8.6%), VNS; 0, surgery		
McGlone et al., 2008[71] Not clear, Canada None	To determine the effects of VNS on cognition and quality of life, compared with other epilepsy treatments Nonrandomized, comparative, and prospective (case-control) 12 months	Inclusion criteria (must meet all): aged over 16; diagnosis of epilepsy; medically uncontrolled CPSs for 5 years or more; did not meet criteria for surgical resection Exclusion criteria (excluded if any criteria met): progressive neurological disease	Total N = 35, comprising 16 in the VNS group, 10 in the surgical group, and 9 in the AED group Sex: 7 of 16 (44%) female, VNS; 6 of 10 (60%) female, surgery; 6 of 9 (67%) female, AEDs Mean age (SD): 35 years (8.0), VNS; 36 years (12.7), surgery; 37 years (6.7), AEDs Mean highest grade: 11 (4.0), VNS; 12 (2.7), surgery; 13 years (2.2), AEDs	• VNS	• Surgery • AEDs
Morrison-Levy et al., 2018[72] Tertiary center, Canada None	To evaluate a cohort of children with both ASD and drug-resistant epilepsy after epilepsy surgery to determine predictors of best outcome Nonrandomized, comparative, and retrospective	Inclusion criteria (must meet all): aged 2 to 18; diagnosis of ASD and drug-resistant epilepsy Exclusion criteria (excluded if any criteria met): < 12 months follow-up	Total N = 29, comprising 14 in the VNS group and 15 in the surgical group One patient underwent corpus callosotomy but it was not clear which group they were allocated to. Sex: 1 of 14 (7%) female, VNS: 3 of 15 (20%) female, surgery	• VNS	• Surgery

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
	Varied, but a minimum of 12 months up to 15 years		Mean age at surgery (range): 12.4 years (5 to 17), VNS; 7.7 years (3 to 13), surgery Mean age at seizure onset (range): 43 months (2 to 120), VNS; 25 months (5 to 96), surgery Type of seizures: 5 of 14 (36%) focal, 9 of 14 (64%) generalized, VNS; 7 of 15 (47%) focal, 8 of 15 (53%) generalized, surgery Mean number of AEDs (SD) prior to surgery: 3.0 (1.0) overall Mean duration of follow-up (range): 42 months (1 to 6 years)		
Nei et al., 2006[73] Epilepsy center, U.S. None	To evaluate VNS and CC Nonrandomized, comparative, and prospective Varied, up to 12.7 years	Inclusion criteria (must meet all): diagnosis of refractory epilepsy with GTC, tonic, or atonic seizures Exclusion criteria (excluded if any criteria met): incomplete data; additional epilepsy surgery	Total N = 78, comprising 25 in the VNS group and 53 in the CC group Sex: 10 of 25 (40%) female, VNS: 17 of 53 (32%) female, CC Mean duration of epilepsy (SD): 32.3 years (12.2), VNS; 22.9 years (9.9), CC Mean age at onset of epilepsy (SD): 11.5 years	• VNS	• CC

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			(12.8), VNS; 7.4 years (5.8), CC GTC Seizure Groups Mean age (range): 44 years (21 to 74), VNS; 32 years (13 to 55), CC Mean follow-up (range): 1.34 years (0.75 to 3.13), VNS; 4.5 years (0.55 to 12.7), CC Type of epilepsy: 57% partial, 42% generalized, VNS; 40% partial, 60% generalized, CC Tonic or Atonic Seizure Groups Mean age (range): 45 years (35 to 58), VNS; 30 years (15 to 48), CC Mean follow-up (range): 1.5 years (0.98 to 2.73), VNS; 4.5 years (0.75 to 12.5), CC		
Ryvlin et al., 2018[75] National registry, U.S.	To assess whether SUDEP rates decrease during the VNS post-implantation follow-up period Retrospective analysis of registry Up to 10 years	Inclusion criteria (must meet all): VNS; diagnosis of epilepsy; U.S. citizen or resident; U.S. Social Security Number; known date of birth Exclusion criteria (excluded if any criteria met): none reported	Total N = 40,433 participants with 277,661 PYs of follow-up Sex: 50% female Mean age at implantation (range): 30.8 years (0 to 89) Median duration of follow-up: 7.6 years	• VNS	• No comparator

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
Sherman et al., 2008[76] Tertiary pediatric hospital, Canada	To investigate QoL changes after VNS in children with epilepsy Nonrandomized, comparative, and retrospective 12 months	Inclusion criteria (must meet all): VNS or chronic epilepsy receiving standard medical treatment; aged 3 to 18; no prior history of VNS for those in the standard medical treatment group Exclusion criteria (excluded if any criteria met): none reported	Total N = 53, comprising 34 in the VNS group and 19 in the no VNS group Mean age (range): 12.3 years (3 to 18), VNS; 9.5 years (4 to 14), no VNS Mean age at onset (range): 3.5 years (0 to 11.6), VNS; 2.8 years (0.08 to 10), no VNS Mean duration of epilepsy (range): 9.4 years (1.7 to 17.5), VNS; 6.8 years (1.5 to 12.8), no VNS Mean number of AEDs (range): 2.1 (1 to 4), VNS; 1.9 (1 to 5), no VNS Mean number of prior AEDs (range): 8.6 (3 to 14), VNS; 3.4 (0 to 10), no VNS Mean number of seizures per month: 173.2 (1 to 1,710), VNS; 96.1 (0 to 900), no VNS Type of epilepsy: 47% localization-related, 50% generalized, 3% undetermined, 0 other, VNS; 80% localization-related, 15% generalized, 0	• VNS	• No VNS

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			undetermined, 5% other, no VNS		
Van Lierde et al., 2015[77] University hospital, Belgium None	To determine the objective vocal quality at rest in people treated with VNS Nonrandomized, comparative, and prospective Not clear, but median time since implantation was 3 years	Inclusion criteria (must meet all): diagnosis of epilepsy; not suitable for resective surgery (VNS group); parents consulting for a vocal problem in their child (no VNS group); no history of neurologic disorders and voice disorders (no VNS group) Exclusion criteria (excluded if any criteria met): none reported	Total N = 26, comprising 13 in the VNS group and 13 in the no VNS group Sex: 46% female, VNS; 46% female, no VNS Mean age (range): 42.8 years (24 to 57), VNS; 42.8 years (24 to 57), no VNS Median time since VNS implantation (range): 3 years (0.3 to 14), VNS	• VNS	• No VNS (gender- and age-matched)
You et al., 2008[55] Epilepsy centers, Korea None	To compare the efficacy and safety of CC and VNS as long-term adjunct therapy in children with Lennox–Gastaut syndrome Nonrandomized, comparative, and retrospective A minimum of 12 months	Inclusion criteria (must meet all):children with uncontrolled seizures; unsuitable for respective surgery Exclusion criteria (excluded if any criteria met): none reported	Total N = 24, comprising 10 in the VNS group and 24 in the CC group Sex: 6 of 10 (60%) female, VNS; 4 of 14 (28.6%) female, CC Note. We have assumed the data are mean and SD, but this was not explicitly stated in the paper. Mean age at seizure onset (SD): 23.6 months (34.0), VNS; 22.1 months (27.5), CC Mean seizure duration prior to surgery (SD): 104.8	• VNS	• CC

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			months (55.5), VNS; 53.9 months (39.4), CC Mean follow-up (SD): 33.0 months (23.1), VNS; 36.9 months (35.2), CC Main seizure type: 4 (40%) head-drop (atonic or tonic), 0 atypical absence, 3 (30%) myoclonic, 2 (20%) generalized tonic, 1 (10%) generalized tonic-clonic, VNS; 13 (93%) head-drop (atonic or tonic), 1 (7%) atypical absence, 0 myoclonic, 0 generalized tonic, 0 generalized tonic-clonic, CC Mean number of AEDs (SD): 2.9 (0.57), VNS; 3.1 months (0.95), CC		
Depression					
Aaronson et al., 2017[56] Conway et al., 2018 [59] Kumar et al., 2019[70] 61 U.S. sites NCT00320372	To determine whether adjunctive VNS with TAU in depression has superior long-term outcomes compared with TAU only Prospective registry 5 years	Inclusion criteria (must meet all): aged 18 or older; have a current MDE (according to DSM-IV-TR criteria and confirmed by MINI) of ≥ 2 years in duration (unipolar or bipolar depression) or have a history of at least 3 depressive episodes including the current	Total N = 795, comprising 335 in the new VNS group, 159 in the group who received VNS treatment in the D-21 study and rolled over into the registry after completing participation in the D-21 study, and 301 in the TAU group	• VNS+TAU	• TAU

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
		MDE; history of inadequate response to at least 4 depression treatments (including maintenance pharmacotherapy, defined as dosage per Physician's Desk Reference labeling for a minimum of 4 weeks, psychotherapy, and ECT); CGI-S score ≥ 4 Exclusion criteria (excluded if any criteria met): history of schizophrenia, schizoaffective disorder, any other psychotic disorder, or a current MDE that included psychotic features; currently psychotic; history of rapid-cycling bipolar disorder; previous use of VNS (other than the D-21 rollover patients)	Total ITT N = 765 (489 VNS+TAU and 276 TAU) for efficacy analyses Total N = 795 (494 VNS+TAU and 301 TAU) for safety analysis Sex: 350 of 494 (71%) female, VNS+TAU; 211 of 301 (70%) female, TAU Race or ethnicity: 478 of 494 (97%) Caucasian, VNS+TAU; 274 of 301 (91%) Caucasian, TAU Past treatment with ECT: 280 of 494 (57%), VNS+TAU; 120 of 31 (40%), TAU Mean age at baseline: 48.9 years, VNS+TAU; 49.9 years, TAU Mean age at initial onset of depression: 20.9 years, VNS+TAU; 21.1 years, TAU Mean age at initial diagnosis of depression: 28.9 years, VNS+TAU; 29.5 years, TAU Mean number of failed treatments for depression: 8.2, VNS+TAU; 7.3, TAU		

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			Mean lifetime number of diagnosed depressive episodes: 14.9, VNS+TAU; 12.0, TAU Mean number of psychiatric hospitalizations within 5 years before enrolment: 3.0, VNS+TAU; 1.9, TAU Mean lifetime number of suicide attempts: 1.8, VNS+TAU; 1.2, TAU Mean MADRS score at baseline: 33.1, VNS+TAU; 29.3, TAU Mean CGI-S score at baseline: 5.2, VNS+TAU; 4.7, TAU Mean QIDS-SR score at baseline: 18.2, VNS+TAU; 15.7, TAU Primary diagnosis of current MDE: moderate recurrent major depression 63 of 494 (13%), VNS+TAU and 69 of 2013 (23%), TAU; severe recurrent major depression 225 of 494 (46%), VNS+TAU and 95 of 301 (32%), TAU; moderate single-episode major depression 16 of 494 (3%), VNS+TAU and 30 of		

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			301 (10%), TAU; severe single-episode major depression 56 of 494 (11%), VNS+TAU and 36 of 301 (12%), TAU; bipolar I disorder, most recent depressive episode of moderate severity 25 of 494 (5%), VNS+TAU and 21 of 301 (7%), TAU; bipolar I disorder, most recent depressive episode of severe severity 62 of 494 (13%), VNS+TAU and 12 of 301 (4%), TAU; bipolar II disorder, most recent episode depressed 47 of 494 (10%), VNS+TAU and 38 of 301 (13%), TAU		
Feldman et al., 2013[61] Medicare claims database, U.S.	To study the health care utilization experience of Medicare beneficiaries implanted with VNS during Medicare coverage, compared with beneficiaries with TRD and managed depression Nonrandomized, comparative, and retrospective Minimum of 2 years	Inclusion criteria (must meet all): 18 years or older; VNS implanted between January 1, 2006 and June 30, 2007 for a diagnosis of depression (VNS); between 8 and 17 medication management visits, and had 2 or more psychiatric hospitalizations (TRD); between 8 and 17 medication management visits, and had at least 1	Total N = 12,853, comprising 690 in the VNS group, 4,639 in the TRD group and 7,524 in the managed depression group Sex: 73% female, VNS; 67% female, TRD; 69% female, managed depression Race or ethnicity: 97% White, VNS; 88% White, TRD; 87% White, managed depression Mean age: 51.9 years, VNS; 56.6 years (95% CI, 56 to	• VNS	• No VNS (TRD and managed depression)

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
		ECT treatment (TRD); 18 or more medication management visits (TRD); diagnosis of depression but did not receive ECT, had no more than one psychiatric hospitalization, and had 8 to 11 medication management visits (managed depression) Exclusion criteria (excluded if any criteria met): claims history of epilepsy; primary diagnosis of bipolar disorder	57), TRD; 58.7 years (95% CI, 58 to 59), managed depression;		
George et al., 2005[62] Rush et al., 2005[74] 22 U.S. sites	To explore the longer-term effects of VNS+TAU compared with TAU Nonrandomized, comparative, and prospective 12 months	Inclusion criteria (must meet all): patients who completed the acute phase (10 weeks) of the randomized controlled trial comparing VNS with sham VNS; for participants who received sham VNS, they requalified if an average score of ≥ 18 on the $HRSD_{24}$ over 2 assessments prior to VNS activation	Total N = 329, comprising 205 in the VNS+TAU group and 124 in the TAU group Mean age (SD): 46.3 years (8.9), VNS+TAU; 45.5 years (10.0), TAU Sex: 64% female, VNS+TAU; 69% female, TAU Race or ethnicity: 97% Caucasian, 2% African American, 0 Asian, 2% Hispanic, < 1% other, VNS+TAU; 90% Caucasian,	• VNA+TAU	• TAU

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
		Exclusion criteria (excluded if any criteria met): none reported For TAU, the inclusion criteria were similar but were more reflective of actual practice (e.g., a history of psychotherapy was not required in the TAU group)	4% African American, 0 Asian, 2% Hispanic, 5% other, TAU Type of depression: unipolar 90%, bipolar 10%, VNS+TAU; unipolar 88%, bipolar 12%, TAU Unipolar type: 87% recurrent, 13% single episode, VNS+TAU (n = 185); 85% recurrent, 15% single episode, TAU (n = 109) Mean duration of current MDE (SD): 49.9 months (52.1), VNS+TAU; 68.6 months (91.5), TAU Chronic (≥ 2 years) current MDE: 68%, VNS+TAU; 69%, TAU Mean number of failed adequate treatments in current MDE (SD): 3.5 (1.3), VNS+TAU; 3.5 (1.3), TAU Mean number of failed adequate treatments in current MDE per year of MDE (SD): 1.6 (1.4), VNS+TAU; 2.4 (5.4), TAU		

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			ECT in lifetime: 53% VNS+TAU; 26%, TAU ECT in current MDE: 35% VNS+TAU; 12%, TAU Mean age at first symptoms (SD): 21.8 years (11.9), VNS+TAU; 20.8 years (11.5), TAU Mean age at definitive diagnosis (SD): 30.8 years (10.5), VNS+TAU; 29.4 years (11.0), TAU Mean duration of illness (SD): 25.5 years (11.9), VNS+TAU; 25.8 years (13.2), TAU Mean length of time since definitive diagnosis (SD): 16.5 years (9.9), VNS+TAU; 17.1 years (9.8), TAU Mean length of time between onset of symptoms and definitive diagnosis (SD): 10.0 years (10.7), VNS+TAU; 9.6 years (10.8), TAU Number of lifetime episodes of depression: 24% 0 to 2, 34% 3 to 5, 27% 6 to 10, 9% > 10, 5% unknown, VNS+TAU; 25% 0 to 2, 29%		

Citation Setting NCT Number	Study Aim Study Design and Duration	Inclusion and Exclusion Criteria	Patient Characteristics	Description of Intervention	Description of Comparator(s)
			3 to 5, 15% 6 to 10, 26% > 10, 6% unknown, TAU Number of lifetime suicide attempts: 68% 0, 17% 1, 7% 2, 4% 3, 2% 4, 2% 5, < 1% 10, 0 12, 0 18, VNS+TAU; 65% 0, 13% 1, 9% 2, 8% 3, 2% 4, 2% 5, 0 10, < 1% 12, < 1% 18, TAU Number of suicide attempts in last 12 months: > 99% 0, < 1% 1, 0 2, 0 3, 0 4, VNS+TAU; 97% 0, 2% 1, 0 2, 0 3, < 1% 4, TAU Treatment induced hypomania or mania: 8%, VNS+TAU; 5%, TAU Mean number of prior hospital admissions for mood disorders (SD): 2.7 (5.4), VNS+TAU; 2.1 (2.9), TAU See Table C14 for use of antidepressant medication		

Abbreviations. AED: antiepileptic drug; ASD: autism spectrum disorder; CC: corpus callosotomy; CGI-S: Clinical Global Impression – Severity; CPS: complex partial seizure; DSM-IV-TR; Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; ECT: electroconvulsive therapy; EEG: electroencephalogram; GTC: generalized tonic-clonic; HRSD; Hamilton Rating Scale Depression; IQR: interquartile range; ITT: intent-to-treat; MADRS: Montgomery-Åsberg Depression Rating Scale; MDE: major depressive episode; MINI: Mini International Neuropsychiatric Interview; MRI: magnetic resonance imaging; NCT: U.S. National Clinical Trial; PY: person-year; QIDS-SR: Quick Inventory of Depressive Symptomatology–Self Report; QoL: quality of life; RNS: responsive neurostimulation; SD: standard deviation; SGS: secondary generalized seizure; SPS: simple partial seizure; SUDEP: sudden unexpected death in epilepsy; TAU: treatment as usual; TRD: treatment-resistant depression; VNS: vagal nerve stimulation.

Table C14. Use of Antidepressant Medications in the Current Major Depressive Disorder (George et al., 2005[62])

Antidepressant Medication	VNS+TAU	TAU	P Value
Heterocyclics/TCAs	50%	39%	*P* = .042
SSRIs	90%	92%	*P* > .05
MAOIs	24%	17%	*P* > .05
Other Antidepressants	94%	97%	*P* > .05
Anticonvulsants	52%	47%	*P* > .05
Stimulants	43%	23%	*P* < .001
Atypical Antipsychotics	42%	35%	*P* > .05
Nonatypical Antipsychotic	11%	4%	*P* = .032
Other	45%	40%	*P* > .05

Abbreviations. MAOI: monoamine oxidase inhibitor; SSRI: selective serotonin reuptake inhibitor; TAU: treatment as usual; TCA: tricyclic antidepressant; VNS: vagal nerve stimulation.

Table C15. Evidence Tables for Nonrandomized and Registry-based Studies

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
Epilepsy				
Amar et al., 2004[57] National registry, U.S. None	Seizure Frequency Median reduction in seizure frequency at 3 months: 42.5%, prior cranial surgery; 47.0%, no prior cranial surgery; *P* = .045 Median reduction in seizure frequency at 6 months: 42.9%, prior cranial surgery; 52.9%, no prior cranial surgery; *P* < .001 Median reduction in seizure frequency at 12 months: 45.7%, prior cranial surgery; 60.0%, no prior cranial surgery; *P* < .001 Median reduction in seizure frequency at 18 months: 52.0%,	Treatment Withdrawal Not reported Mood or Cognitive Changes At 3 months, patients in the no prior cranial surgery group reported improved mood more often than patients in the prior cranial surgery group (*P* < .001) At 3 months, patients in the no prior cranial surgery group reported improved memory more often than	Harms Not reported Reimplantation Not reported Failure Rate Not reported	No other relevant outcomes reported

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	prior cranial surgery; 62.7%, no prior cranial surgery; *P* >.05 Median reduction in seizure frequency at 24 months: 50.5%, prior cranial surgery; 66.7%, no prior cranial surgery; *P* = .009 Response of at least a 50% reduction in seizure frequency at 12 months: 47.6%, prior cranial surgery; 58.0%, no prior cranial surgery; *P* < .001 Response of at least a 75% reduction in seizure frequency at 12 months: 28.5%, prior cranial surgery; 37.1%, no prior cranial surgery; *P* = .002 Response of at least a 90% reduction in seizure frequency at 12 months: 14.1%, prior cranial surgery; 21.6%, no prior cranial surgery; *P* = .001 Response of at least a 50% reduction in seizure frequency at 24 months: 55.1%, prior cranial surgery; 62.2%, no prior cranial surgery; *P* > .05 Response of at least a 75% reduction in seizure frequency at 24 months: 31.4%, prior cranial surgery; 43.7%, no prior cranial surgery; *P* = .009	patients in the prior cranial surgery group (*P* = .02) At 3 months, patients in the no prior cranial surgery group reported improved verbal communication more often than patients in the prior cranial surgery group (*P* = .01) At 24 months, both groups reported similar levels of improvement in mood, memory, and verbal communication Quality of Life At 3 months, statistically significant improvements in other areas (alertness, school and professional achievements, postictal state, seizure clustering) were observed in the no prior cranial surgery group compared with the prior cranial surgery group At 24 months, both groups showed similar improvements, with a statistically significant difference seen only for alertness (*P* = .04)		

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	Response of at least a 90% reduction in seizure frequency at 24 months: 17.3%, prior cranial surgery; 26.8%, no prior cranial surgery; *P* = .02 Seizure Freedom 100% reduction in seizure frequency at 12 months: 4.1%, prior cranial surgery; 6.9%, no prior cranial surgery; *P* > .05 100% reduction in seizure frequency at 24 months: 5.1%, prior cranial surgery; 8.3%, no prior cranial surgery; *P* > .05 For patients who failed lobectomy, median reduction in seizure activity was 36.0% at 3 months, 33.8% at 6 months, 38.7% at 12 months, 50.7% at 18 months, and 62.5% at 24 months of VNS For patients who failed corpus callosotomy, median reduction in seizure activity was 51.3% at 3 months, 51.4% at 6 months, 55.7% at 12 months, 50.0% at 18 months, and 32.1% at 24 months of VNS For patients failing all other cranial operations, median reduction in seizure activity was			

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	40.0% at 3 months, 50.0% at 6 months, 45.5% at 12 months, 61.9% at 18 months, and 75.0% at 24 months of VNS Seizure Severity Not reported Seizure Duration Not reported			
Boon et al., 2002[58] University hospital, Belgium None	Seizure Frequency Mean change in CPSs from 21 per month (range, 2 to 180) to 7 per month (range, 0 to 20) after VNS (*P* = .02) Mean change in CPSs from 6 per month (range, 1 to 17) to < 1 per month (range, 0 to 4) after surgery (*P*< .001) Mean change in CPSs from 12 per month (range, 1 to 30) to 9 per month (range, 0 to 30) after a change in AED treatment (*P* = .21) Patients in the VNS (*P* = .002) and surgical groups (*P*< .001) had greater improvements in seizure frequency than those in the AED group Seizure Freedom In the VNS group, 6 patients became seizure-free of CPSs,	Treatment Withdrawal Not reported Mood or Cognitive Changes Not reported Quality of Life Not reported	Harms Not reported Reimplantation Not reported Failure Rate Not reported	No other relevant outcomes reported

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	with 3 of these continuing to have SPSs In the surgical group, 23 patients became seizure-free (CPSs) In the AED group, 1 patient became seizure free Seizure Severity Not reported Seizure Duration Not reported			
Ellens et al., 2018[60] Not clear, U.S. None	Seizure Frequency Median number of seizures per month after treatment (IQR): 1.3 (6.3), VNS; 2.5 (29.8), RNS; *P* = .58 Median reduction in seizures (IQR): 66% (47.5), VNS; 58% (80.2), RNS; *P* = .87 Seizure Freedom Seizure freedom: 2 of 13 (15.4%), VNS; 4 of 17 (23.5%), RNS; *P* = .67 Seizure Severity Not reported Seizure Duration Not reported	Treatment Withdrawal Not reported Mood or Cognitive Changes Not reported Quality of Life Not reported	Harms Total complications: 2 of 13 (15.4%), VNS; 3 of 17 (17.6%), RNS 2 patients in the VNS experienced temporary hoarseness 1 patient in the RNS group experienced infection and wound revision, and 1 experienced other complications, but no details were reported No deaths were observed in either group Reimplantation Not reported Failure Rate Not reported	No other relevant outcomes reported

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
Gonen et al., 2015[63] Medical center, Israel None	Seizure Frequency See Table C16 for seizure frequency Mean seizure frequency at follow-up (SD): 2.94 (1.12), VNS; 2.38 (1.31), AED; *P* = .047 Mean change in seizure frequency from baseline to follow-up (SD): from 3.52 (0.67) to 2.94 (1.12), *P* = .006, VNS; from 3.15 (0.72) to 2.38 (1.31), *P* < .001, AED Seizure Freedom See Table C16 for seizure freedom Seizure Severity Not reported Seizure Duration Not reported	Treatment Withdrawal Not reported Mood or Cognitive Changes Not reported Quality of Life Not reported	Harms Not reported Reimplantation Not reported Failure Rate Not reported	Mean number of AEDs at follow-up (SD): 3.31 (1.09), VNS; 2.57 (1.08), AED; *P* = .007 Mean change in number of AEDs from baseline to follow-up (SD): from 2.91 (0.96) to 3.31 (1.09), *P* = .02, VNS; from 2.32 (0.98) to 2.57 (1.08), *P* = .14, AED
Harden et al., 2000[64] University hospital, U.S. None	Seizure Frequency Mean change in seizures per month from baseline to end of study (SD): from 16.2 (19.4) to 8.9 (13.2), VNS; from 3.2 (7.4) to 2.0 (3.3), AED Seizure change over time was significantly different between groups *P* = .01 In the VNS group, 15 (75%) reported a reduction in seizures,	Treatment Withdrawal Not reported Mood or Cognitive Changes See Table C17 Quality of Life Not reported	Harms Not reported Reimplantation Not reported Failure Rate Not reported	No difference in mood was seen between responders and nonresponders

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	1 (5%) reported an increase, and 4 (20%) reported no change In the AED group, 6 (30%) reported a reduction in seizures, 5 (25%) reported an increase, and 9 (45%) reported no change Response (defined as > 75% reduction): 5 (25%), VNS; 1 (5%) AED Response (defined < 50% reduction): 4 (20%), VNS; 1 (5%) AED Response (defined as a 50 to 75% reduction): 5 (25%), VNS; 2 (10%) AED Seizure Freedom In the VNS group, 1 participant (5%) became seizure free In the AED group, 2 participants (10%) became seizure free Seizure Severity Not reported Seizure Duration Not reported			
Helmers et al., 2003[65] National registry, U.S.	Seizure Frequency Median seizure frequency reduction at 3 months (range): 25% (-100% to 100%), early	Treatment Withdrawal Not reported Mood or Cognitive Changes Not reported	Harms Not reported Reimplantation Not reported Failure Rate	Mean number of AEDs (SD): 2.0 (1.1), early treatment; 2.1 (1.2), late treatment

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
None	treatment; 40% (-100% to 100%), late treatment Median seizure frequency reduction at 12 months (range): 50% (-100% to 100%), early treatment; 57% (-100% to 100%), late treatment Reductions were statistically significant in both groups (P = .04), but were not statistically significant between groups at any time point (P = .4) See Table C18 for more results Seizure Freedom See Table C18 Seizure Severity Not reported Seizure Duration Not reported	Quality of Life Not reported	Not reported	
Hoppe et al., 2013[66] Not clear, Germany None	Seizure Frequency See Table C19 Seizure Freedom See Table C19 Seizure Severity See Table C19 for severity measures (Note: severity was not measured using validated instruments) Seizure Duration	Treatment Withdrawal Not reported Mood or Cognitive Changes No significant differences were seen between groups on most measures, although participants in the VNS group reported higher rates of anxiety (50% vs. 20%; P = .047)	Harms Not reported Reimplantation Not reported Failure Rate Not reported	No other relevant outcomes reported

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	Not reported	Quality of Life No significant differences were seen between groups on most measures, although participants in the VNS group reported higher satisfaction with their living conditions (4.1 vs. 3.1; *P* = .04)		
Jamy et al., 2019[67] Neuromodulation clinic, U.S. None	Seizure Frequency In the VNS group, 12 of 27 (44%) reported > 60% reduction in seizures and 4 of 27 (15%) reported < 30% reduction in seizures (defined as nonresponse) In the RNS group, 11 of 16 (69%) reported > 60% reduction in seizures and 1 of 16 (6%) reported < 30% reduction in seizures (defined as nonresponse) Seizure Freedom In the VNS group, no patients became seizure free In the RNS group, 4 of 16 (25%) patients became seizure free Seizure Severity Not reported Seizure Duration Not reported	Treatment Withdrawal Not reported Mood or Cognitive Changes Not reported Quality of Life Not reported	Harms In the VNS group, 11 of 27 (41%) reported increased cough and hoarseness, which were transient In the VNS group, 1 patient had symptomatic partial vocal cord paralysis attributed to chronic VNS implantation, and the device was turned off In the RNS group, 1 patient had probable SUDEP and 1 patient reported transient eye and facial twitching which resolved after decreasing the stimulation level Reimplantation During the study period, 7 of 27 (25%) had a new implant Failure Rate Not reported	No other relevant outcomes reported

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
Kawai et al., 2017[68] National registry, Japan None	Seizure Frequency Not relevant (harms only) Seizure Freedom Not relevant (harms only) Seizure Severity Not relevant (harms only) Seizure Duration Not relevant (harms only)	Treatment Withdrawal Not relevant (harms only) Mood or Cognitive Changes Not relevant (harms only) Quality of Life Not relevant (harms only)	Harms See Tables C20 and C21 for harms over time and detailed numbers of patients Adverse events were as anticipated, occurred most frequently on stimulation, and tended to reduce over time 14 of 385 (3.6%) died • n = 6 SUDEP • n = 1 rectal cancer • n = 1 lung cancer • n = 1 primary brain tumor • n = 1 pneumonia • n = 1 subarachnoid hemorrhage • n = 1 drowning whilst bathing • n = 1 suffocation due to a secondary generalized seizure • n = 1 not reported Reimplantation Not reported Failure Rate 13 of 385 (3.4%) had the VNS explanted • n = 6 infection • n = 6 high lead impedance • n = 1 for an MRI	No other relevant outcomes reported

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
Kuba et al., 2013[69] University medical center, Czechia None	Seizure Frequency See Tables C22 and C23 Mean reduction in seizures at 2 years: 60.3%, VNS; 51.3%, surgery; *P* = .34 Mean reduction in seizures at 2 years: 62.9%, VNS; 60.3%, surgery; *P* = .20 Seizure Freedom See Table C23 Seizure Severity Not reported Seizure Duration Not reported	Treatment Withdrawal Not reported Mood or Cognitive Changes Not reported Quality of Life Not reported	Harms Not reported Reimplantation Not reported Failure Rate Not reported	In the VNS group, no patients completely withdrew from AEDS, 1 (2.9%) withdrew from at least 1 AED, 13 (37.1%) patients had no change in AEDS, and 21 (60%) had other treatment added on In the surgery group, 1 (3.8%) patient completely withdrew from AEDS, 5 (19.2%) withdrew from at least 1 AED, 6 (23.2%) patients had no change in AEDS, and 14 (53.8%) had other treatment added on
McGlone et al., 2008[71] Setting not clear None	Seizure Frequency No comparative data reported Seizure Freedom No comparative data reported Seizure Severity Not reported Seizure Duration Not reported	Treatment Withdrawal Not reported Mood or Cognitive Changes Results reported graphically Participants in all groups had similar memory and depression scores (*P*> .05) Quality of Life Results reported graphically	Harms Not reported Reimplantation Not reported Failure Rate Not reported	In the VNS group, QoL was not related to seizure reduction

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
		Participants in all groups had similar levels of QoL ($P > .05$), although the surgery group did have a higher self-reported QoL than the other 2 groups		
Morrison-Levy et al., 2018[72] Tertiary center, Canada None	Seizure Frequency In the VNS group, 7 of 14 (50%) had an improvement in seizure outcomes (defined as Engel classes II and III) and 7 of 14 (50%) had no worthwhile improvement (defined as Engel class IV) In the surgical group, 10 of 15 (67%) had an improvement in seizure outcomes (defined as Engel classes II and III) and 3 of 15 (20%) had no worthwhile improvement (defined as Engel class IV) 50% of participants in the VNS group had an improvement in seizure frequency (Engel classes I, II, and II combined) and 50% in Engel class IV compared with 80% of participants in the surgery group with an improvement and 20% in Engel class IV; P = .13 Seizure Freedom	Treatment Withdrawal Not reported Mood or Cognitive Changes Not reported Quality of Life Not reported	Harms Not reported Reimplantation Not reported Failure Rate Not reported	Mean number of AEDs after surgery (SD): 1.8 (1.2) overall

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	Seizure freedom (defined as Engel class I): 0, VNS; 10 (66.67%) When compared with the numbers of participants who did not become seizure free, surgery was more effective than VNS (P < .001). Seizure Severity Not reported Seizure Duration Not reported			
Nei et al., 2006[73] Epilepsy center, U.S. None	Seizure Frequency Reduction of 50% or more in seizure frequency: 40%, VNS; 79%, CC; *P* < .001 Reduction of 80% or more in seizure frequency: 20%, VNS; 57%, CC; *P* = .007 In the VNS group, 72% had an Engel class IV outcome, and 28% had an Engel class III outcome In the CC group, 17% had an Engel class I outcome, 8% Engel class II, 42% Engel class III, and 31% had an Engel class IV outcome Seizure Freedom	Treatment Withdrawal Not reported Mood or Cognitive Changes Not reported Quality of Life Not reported	Harms Note: these may not all be directly attributed to the intervention In the VNS group, no patients died In the CC group, 6 patients died (1 in the immediate post-operative period, 4 of SUDEP, and 1 of pneumonia) Complications: 8%, VNS; 21%, CC Complications in the VNS group (1 site infection, 1 defective battery) tended to be less serious than those in the CC group (1 death, 1 status epilepticus, 1 infection, 3	In the GTC-VNS group, 50% had a 50% or greater decrease in GTC seizure frequency and 33% had an 80% or greater reduction In the GTC-CC group, 79.5% had a 50% or greater decrease in GTC seizure frequency and 60% had an 80% or greater reduction No statistically significant differences were seen between the proportion of responders between GTC-VNS and GTC-CC

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	No patients in the VNS group and 17% in the CC group had an Engel class I outcome Seizure Severity Not reported Seizure Duration Not reported		hemiparesis, 2 gait difficulty, 2 disconnection syndrome, and 1 deep venous thrombosis) Most resolved or improved with only 2 (3.5%) of CC patients having permanent sequelae Reimplantation Not reported Failure Rate Not reported	Change in mean seizure frequency per month GTC: 5.0 to 2.2, VNS; *P* = 0.16 Change in mean seizure frequency per month GTC: 17.5 to 3.9, CC; *P* = 0.001 In the GTC-VNS group, 71% of people with partial seizures and 20% of people with generalized epilepsy had a 50% or greater reduction in seizure frequency In the GTC-CC group, 82% of people with partial seizures and 78% of people with generalized epilepsy had a 50% or greater reduction in seizure frequency Change in mean seizure frequency per month in people with partial epilepsy: 8.9 to 2.0, GTC-VNS; 4.6 to 0.5, GTC-CC Change in mean seizure frequency per month in

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
				people with generalized epilepsy: 1.6 to 2.8, GTC-VNS; 23.0 to 4.5, GTC-CC In the GTC-CC group, 100% of people with idiopathic generalized epilepsy had a 50% or greater reduction in seizure frequency In the GTC-VNS group, no patients had idiopathic generalized epilepsy In the Tonic/Atonic-VNS group, 66.7% had a 50% or greater decrease in GTC seizure frequency and 16.7% had an 80% or greater reduction In the Tonic/Atonic-CC group, 77.8% had a 50% or greater decrease in GTC seizure frequency and 61% had an 80% or greater reduction Mean seizure frequency changed from 36.3 to 2.1 seizures/month (P = .003) in the CC

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
				group, and from 10.8 to 6.6 seizures per month (P = 0.25) in the VNS group for people with tonic or atonic seizures
Ryvlin et al., 2018[75] National registry, U.S. None	Seizure Frequency Not relevant (harms only) Seizure Freedom Not relevant (harms only) Seizure Severity Not relevant (harms only) Seizure Duration Not relevant (harms only)	Treatment Withdrawal Not relevant (harms only) Mood or Cognitive Changes Not relevant (harms only) Quality of Life Not relevant (harms only)	Harms 3,689 of 40,433 (9%) died All-cause mortality rate: 13.3 per 1,000 person years (95% CI, 12.9 to 13.7) Age- and gender-adjusted SMR: 4.58 (95% CI, 4.43 to 4.73) Of the 3,689 who died, 632 were SUDEP, with 38 (4%) classified as definite SUDEP; 63 (7%) as probable SUDEP, and 531 (56%) as possible SUDEP Overall crude SUDEP rate: 2.28 per 1,000 person years (95% CI, 22.10 to 2.46) See Table C24 for SUDEP rates over time Reimplantation Not reported Failure Rate 2,864 of 40,433 (7%) had the VNS device explanted or turned off	No other relevant outcomes reported

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
Sherman et al., 2008[76] Tertiary pediatric hospital, Canada None	Seizure Frequency No comparative data reported Seizure Freedom No comparative data reported Seizure Severity Not reported Seizure Duration Not reported	Treatment Withdrawal Not reported Mood or Cognitive Changes Not reported Quality of Life See Tables C25 and C26 for details No significant changes were seen comparing baseline and retest scores in either group	Harms Not reported Reimplantation Not reported Failure Rate Not reported	No differences were seen between responders and nonresponders in QoL or demographics.
Van Lierde et al., 2015[77] University hospital, Belgium None	Seizure Frequency Not reported Seizure Freedom Not reported Seizure Severity Not reported Seizure Duration Not reported	Treatment Withdrawal Not reported Mood or Cognitive Changes Not reported Quality of Life Participants in the VNS group reported significantly higher impacts of their vocal problem on their physical, functional, and emotional quality of life than people in the no VNS group ($P < .05$)	Harms See Quality of Life In the VNS group, 7 of 13 (54%) experienced vocal discomfort of the self-perceived vocal quality on their quality of life In the no VNS group, no participants experienced vocal discomfort of the self-perceived vocal quality on their quality of life In the VNS group, participants were assessed as having a moderate grade of hoarseness, roughness, and the slight presence of breathiness	No other relevant outcomes reported

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
			In the no VNS group, no participants were assessed as having any vocal problems Participants in the VNS group were assessed as having significantly more hoarseness, roughness, breathiness, and strained vocal characteristics than participants in the no VNS group Participants in the VNS group had a significantly lower vocal quality, measured using the Dysphonia Severity Index, than participants in the no VNS group Reimplantation Not reported Failure Rate Not reported	
You et al., 2008[55] Epilepsy centers, Korea None	Seizure Frequency In the VNS group, 7 of 10 (70%) had > 50% reduction in seizure frequency, and 2 of 10 (20%) had > 75% reduction In the CC group, 9 of 14 (64.3%) had > 50% reduction in seizure frequency, and 5 of 14 (35.7%) had > 75% reduction	Treatment Withdrawal Not reported Mood or Cognitive Changes Not reported Quality of Life Not reported	Harms In the VNS group, 2 of 10 (20%) had complications In the VNS group, dyspnea during sleep was noted in 1 patient and drooling in 1 patient. These complications were transient and tolerable and could be controlled by simple adjustment of VNS parameters	There were no significant differences between the 2 groups in efficacy in head-drop reduction. Possible selective treatment effects on other seizure types could not be compared because of the small group sizes

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	There were no significant differences between the 2 groups Seizure Freedom In the VNS group, 2 of 10 (20%) became seizure free In the CC group, 4 of 14 (28.6%) became seizure free No significant differences between groups for rates of seizure freedom (*P* = .51) Seizure Severity Not reported Seizure Duration Not reported		Complications of the corpus callosotomy treatment included aphasia in 1 patient, ataxia in 1 patient, and paresis 1 patient No significant differences between groups for complication rates (*P* = .39) Reimplantation Not reported Failure Rate Not reported	Change of AEDs: 6 of 10 (60%) unchanged, 2 of 10 (20%) decreased, 2 of 10 (20%) increased, VNS; 9 of 14 (64%) unchanged, 2 of 14 (14%) decreased, 3 of 14 (21%) increased, CC
Depression				
Aaronson et al., 2017[56] Conway et al., 2018 [59] Kumar et al., 2019[70] 61 U.S. sites NCT00320372	Depression Severity Not reported Mortality Deaths: 7 (1.4%), VNS+TAU; 8 (2.7%), TAU All-cause mortality per 1,000 person-years: 3.53 (95% CI, 1.41 to 7.27), VNS+TAU; 8.63 (95% CI, 3.72 to 17.01), TAU Suicides: 2 (0.4%) VNS+TAU; 2 (0.7%), TAU Suicides per 1,000 person-years: 1.01 (95% CI, 0.11 to 3.64),	Treatment Withdrawal VNS+TAU: 461 (93%) at 1 year, 289 (59%) at 2 years, 313 (63%) at 3 years, 334 (68%) at 4 years, and 300 (61%) at 5 years TAU: 224 (74%) at 1 year, 185 (62%) at 2 years, 168 (56%) at 3 years, 149 (50%) at 4 years, and 138 (46%) at 5 years Compliance with Other Depression Treatment Not reported	Harms The frequency, intensity, and burden of side effects was similar between VNS+TAU and TAU at baseline and these decreased over time in both groups. Reimplantation Not reported Failure Rate Not reported	Subgroup Analyses See also Table C27 for results by prior ECT response Significant differences (*P* < .05) were seen within each comparator arm grouped by baseline comorbid anxiety or by unipolar vs. bipolar depression (reported graphically). QoL improvements were also seen for both

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	VNS+TAU; 2.20 (95% CI, 0.24 to 7.79), TAU Suicidal Ideation and Severity OR of a score of 2 or 3 on QIDS-SR item 12 (corresponding to the responses "think of suicide or death several times a week for several minutes" to "have actually tried to take my life"): 2.11 (95% CI, 1.28 to 3.48) OR of a response of "yes" to the question "Has the patient made a suicidal gesture or attempt since the last visit?": 2.04 (95% CI, 1.08 to 3.86) OR of a score ≥ 4 on MADRS item 10 (corresponding to the responses "probably better off dead" and "active preparations for suicide"): 1.67 (95% CI, 0.98 to 2.83) Response and Duration of Response Response (cumulative) at 5 years, defined as a reduction of ≥ 50% from baseline MADRS score at any postbaseline visit: 67.6% (95% CI, 63.4% to 71.7%), VNS+TAU; 40.9% (95% CI, 35.4% to 47.1%). TAU; *P* < .001	Cognitive Changes Not reported Quality of Life Analysis excluded patients who rolled over from the D-21 study and patients who were not depressed at baseline QoL was improved in the VNS+TAU group at 3 months compared with TAU (reported graphically; *P* value not reported) and was sustained over the 5 years The change in QoL corresponded to a change in MADRS score of 34% (lower than the usual MID of 50% change from baseline) Sleep Not reported		people with unipolar and bipolar depression, although the effect for bipolar depression was not statistically significant. In a modified dataset (excluding participants rolled over from the D-21 study and participants with a MADRS score of < 10 at baseline, 205 of 328 (62.5%) had a first response during the 5 years in the VNS+TAU group compared with 108 of 271 (39.9%) in the TAU group See Table C28 for probability estimates for response Median time to first response (IQR): 18.1 months (3.9 to 49.1), VNS+TAU; 49.1 months (12.3 to not estimable), TAU (*P* < .01) HR for time to first response: 2.0 (95% CI, 1.6 to 2.5) for

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	Response (cumulative) at 5 years, defined as a CGI-I score of 1 or 2 at any postbaseline visit: 75.9% (95% CI, 72.3% to 79.9%), VNS+TAU; 48.6% (95% CI 43.0% to 54.8%). TAU; *P* < .001 Response (cumulative), defined as a reduction of ≥ 50% from baseline QIDS-SR score at any postbaseline visit: 64.7% (95% CI, 60.7% to 69.2%), VNS+TAU; 41.7% (95% CI 35.9% to 47.5%). TAU; *P* < .001 Median time to first response, based on MADRS score: 12 months, VNS+TAU; 48 months; TAU; *P* < .001 Median time to recurrence, based on MADRS score: 12 months, VNS+TAU; 7 months; TAU; *P* < .001 Median time to first response, based on QIDS-SR score: 22 months, VNS+TAU; 47 months; TAU; *P* < .001 Median time to recurrence, based on QIDS-SR score: 10 months, VNS+TAU; 4 months; TAU; *P* = .14			VNS+TAU compared with TAU In the VNS+TAU group, 148 of 205 (72.2%) had a first response in the first year In the TAU group, 69 of 108 (63.9%) had a first response in the first year In the VNS+TAU group, 98 of 148 (66.2%) relapsed from their first response during the study In the TAU group, 55 of 69 (79.7%) relapsed from first response during the study. When response occurred within the first 12 months of initiating treatment, time to relapse took 1 year or longer for 47% of the responders in the VNS+TAU group compared to 39% of the responders in the TAU group.

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	Remission and Duration of Remission Remission (cumulative) at 5 years, defined as a MADRS score ≤ 9 at any postbaseline visit: 43.3% (95% CI, 38.9% to 47.7%), VNS+TAU; 25.7% (95% CI 20.7% to 31.1%). TAU; *P* < .001 Remission (cumulative) at 5 years, defined as a QIDS-SR score ≤ 5 at any postbaseline visit: 40.4% (95% CI, 36.2% to 44.9%), VNS+TAU; 25.0% (95% CI 19.9% to 30.1%). TAU; *P* < .001 Remission (cumulative) at 5 years, defined as a CGI-I score of 1 at any postbaseline visit: 49.7% (95% CI, 45.5% to 54.3%), VNS+TAU; 21.4% (95% CI, 16.7% to 26.4%). TAU; *P* < .001 Median time to remission, based on MADRS score: 49 months, VNS+TAU; 65 months; TAU; *P* < .001 Duration of remission, based on MADRS score: 40 months, VNS+TAU; 19 months; TAU; *P* = .10) Duration of remission, based on QIDS-SR score: 30 months,			Median time to relapse from first response in first year (IQR): 10.1 months (4.2 to 31.5), VNS+TAU; 7.3 months (3.1 to 17.6), TAU (*P* < .01) HR for time to relapse: 0.6 (95% CI, 0.4 to 0.9) for VNS+TAU compared with TAU The probability of retaining the first response beyond the first 12 months was similar between VNS+TAU and TAU (*P* = 1.00) The probability and timing of a second response after relapse was similar between VNS+TAU and TAU, but the durability of second response may be higher in the VNS+TAU group compared with TAU (*P* = .06) See Table C28 for detailed probabilities

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	VNS+TAU; 18 months; TAU; *P* = .20) Anxiety Not reported			
Feldman et al., 2013[61] Medicare claims database, U.S. None	Depression Severity Not reported Mortality See Table C29 In the VNS population, 37 patients (5%) died during the 2-year post-implantation study period Suicidal Ideation and Severity Suicide attempt or self-inflicted injury: 10% in year 1, 15% in year 2, VNS; 7%, TRD; 1%, managed depression Suicide ideation: 8% in year 1, 14% in year 2, VNS; 6%, TRD; 1%, managed depression Response and Duration of Response Not reported Remission and Duration of Remission Not reported Anxiety Anxiety, obsessive compulsive disorders, phobias: 11% in year	Treatment Withdrawal Not reported Compliance with Other Depression Treatment Not reported Cognitive Changes Not reported Quality of Life Not reported Sleep Not reported	Harms In the VNS group, 150 of 629 (24%) experienced no negative events (defined as no emergency room use, no psychiatric hospitalizations, no hospitalization for poisoning, no ECT, no diagnoses for poisoning, self-injury, self-harm, or suicidal ideation) In the VNS group, 197 of 629 (31%) experienced a negative event (defined as any amount of ECT postimplantation, two or more psychiatric hospitalizations (could include psychiatric as well as hospitalization for a poisoning or other self-harm/ suicidal ideation diagnosis, or two or more diagnoses on claims of poisoning, suicidal ideation, self-harm, or self-injury) In the first and second year post-identification period, 1,429 of 3,797 in the TRD group (38%) had no negative events	No other relevant outcomes reported

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	1, 16% in year 2, VNS; 59%, TRD; 43%, managed depression		and 767 (20%) had negative events In the first and second year post-identification period, 2,979 of 6,005 in the managed depression group (50%) had no negative events and 219 (4%) had negative events Reimplantation Not reported Failure Rate Not reported	
George et al., 2005[62] Rush et al., 2005[74] 22 U.S. sites None	Depression Severity Mean reduction in total IDS-SR per month was 0.40 points greater for participants in the VNS+TAU group compared with those in the TAU group (*P*< .001) which increased over time See Table C30 for depression severity over time Mortality No comparative data reported Suicidal Ideation and Severity No comparative data reported Response and Duration of Response See Table C31 16 of the 29 (55.2%) responders at 3 months in the VNS+TAU	Treatment Withdrawal Not reported Compliance with Other Depression Treatment Not reported Cognitive Changes Not reported Quality of Life Not reported Sleep Not reported	Harms No comparative data reported Reimplantation Not reported Failure Rate Not reported	Subgroup Analyses Overall $IDS\text{-}SR_{30}$ response rate (12 months) in people with MDD: 34 of 163 (21%), VNS+TAU; 12 of 97 (12%), TAU Overall $IDS\text{-}SR_{30}$ response rate (12 months) in people with bipolar disorder: 5 of 17 (29%), VNS+TAU; 1 of 15 (7%), TAU Overall $HRSD_{24}$ response rate (12 months) in people with MDD: 49 of 164 (30%), VNS+TAU; 11 of 91 (12%), TAU

Citation Setting NCT Number	Condition-specific Outcomes	Secondary Outcomes	Safety	Other
	group were also responders at 12 months 1 of the 7 (14.3%) responders at 3 months in the TAU group were also responders at 12 months 25 of the 174 (14.4%) nonresponders at 3 months in the VNS+TAU group became responders at 12 months 13 of the 113 (11.5%) nonresponders at 3 months in the TAU group became responders at 12 months No *P* values were reported Remission and Duration of Remission See Table C31 Anxiety Not reported			Overall $HRSD_{24}$ response rate (12 months) in people with bipolar disorder: 5 of 17 (29%), VNS+TAU; 2 of 13 (15%), TAU No *P* values were reported

Abbreviations. AED: antiepileptic drug; CC: corpus callosotomy; CGI-I: Clinical Global Impression - Improvement scale; CI: confidence interval; CPS: complex partial seizure; ECT: electroconvulsive therapy; GTC: generalized tonic-clonic; HR: hazard ratio; HRSD: Hamilton Rating Scale of Depression; IDS-SR: Inventory of Depressive Symptomatology Self Report; IQR: interquartile range; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; MID: minimal important difference; NCT: U.S. National Clinical Trial; OR: odds ratio; QIDS-SR: Quick Inventory of Depressive Symptomatology – Self Report version; RNS: responsive neurostimulation; QoL: quality of life; SD: standard deviation; SMR: standardized mortality rate; SPS: simple partial seizure; SUDEP: sudden unexpected death in epilepsy; TAU: treatment as usual; TRD: treatment-related depression; VNS: vagal nerve stimulation.

Table C16. Change in Seizure Frequency by Treatment Group (Gonen et al., 2015[63])

Frequency	VNS		AED	
	Baseline	Follow-Up	Baseline	Follow-Up
1 or More Seizures per Day	20 (60.61%)	12 (36.36%)	15 (31.91%)	9 (19.15%)
1 or More Seizures per Week	10 (30.30%)	12 (36.36%)	25 (53.19%)	17 (36.17%)
1 or More Seizures per Month	3 (9.09%)	6 (18.18%)	6 (12.77%)	12 (25.53%)
1 or More Seizures During the Last 3 Months (but not within the past month)	0	1 (3.03%)	1 (2.13%)	1 (2.13%)
Seizure-Free (no seizures during the past 3 months)	0	2 (6.06%)	0	0

Abbreviations. AED: antiepileptic drug; VNS: vagal nerve stimulation.

Table C17. Mood and Anxiety Scores by Treatment Group (Harden et al., 2000[64])

Outcome	VNS		*P* Value	AED		*P* Value	*P* Value Between Groups
	Baseline Mean (SD)	End of Study Mean (SD)		Baseline Mean (SD)	End of Study Mean (SD)		
CDRS	20.4 (10.2)	14.8 (9.6)	*P* = .001	23.2 (13.1)	21.2 (10.7)	*P* = .30	*P* = .13
BDI	12.0 (8.8)	9.4 (8.6)	*P* = .04	10.5 (9.3)	10.8 (8.3)	*P* = .87	*P* = .07
HAM-D	12.9 (8.2)	8.8 (6.0)	*P* = .02	12.8 (8.8)	11.3 (6.4)	*P* = .31	*P* = .29
HAM-A	7.2 (5.8)	6.2 (4.2)	*P* = .28	11.7 (9.7)	9.4 (6.9)	*P* = .11	*P* = .54

Abbreviations. AED: antiepileptic drug; BDI: Beck Depression Inventory; CDRS: Cornell Dysthymia Rating Scale; HAM-A: Hamilton Rating Scale for Anxiety; HAM-D: Hamilton Rating Scale for Depression; SD: standard deviation; VNS: vagal nerve stimulation.

Table C18. Seizure Frequency Reduction by Treatment Group (Helmers et al., 2003 Helmers et al., 2003[65])

Time	Treatment Group	≥ 50% Reduction	P Value	≥ 75% Reduction	P Value	≥ 90% Reduction	P Value	≥ 100% Reduction	P Value
3 Months	Early	20 (39.2%)	*P* > .05	12 (23.5%)	*P* > .05	6 (11.8%)	*P* > .05	4 (7.8%)	*P* > .05
	Late	160 (45.2%)		88 (24.9%)		39 (11.0%)		13 (3.7%)	
12 Months	Early	26 (51.0%)	*P* > .05	18 (35.3%)	*P* > .05	12 (23.5%)	*P* > .05	6 (11.8%)	*P* = .03
	Late	204 (57.6%)		117 (33.1%)		60 (17.0%)		16 (4.5%)	

Table C19. Seizure Outcomes by Treatment Group (Hoppe et al., 2013[66])

Outcome	VNS N = 20	AED N = 20	P Value
Self-Reported Seizure Status at Follow-Up			
Seizure Free	1 (5%)	4 (20%)	
Auras Only	0	0	*P* = .15
Continued Seizures	19 (95%)	16 (80%)	
Free of 'Big Seizures'	4 (20%)	12 (60%)	*P* = .01
Maximum Interval of Seizure-free Days (if not seizure free) (SD)	18.1 (14.0)	19.8 (16.0)	*P* = .71
Mean Number of 'Small Seizures' per Month (SD)	4.4 (5.8)	3.6 (3.4)	*P* = .96
Mean Number of 'Big Seizures' per Month (SD)	2.8 (4.4)	1.5 (2.6)	*P* = .11
Mean Total Monthly Seizure Frequency	7.2 (8.4)	5.0 (4.8)	*P* = .59
Objective Change at Follow-Up (from medical charts)			
Mean Reduction in 'Big Seizures' per Month (median)	65.% (80.9)	59.8% (100)	*P* = .72
Mean Reduction in Total Seizures per Month (median)	39.8% (64.9)	-97.6% (-6.8%)	*P* = .052
Seizures Worsened	2 (10%)	8 (40%)	
Seizures Unchanged	6 (30%)	5 (25%)	
Response > 50%	4 (20%)	1 (5%)	*P* = .004
Good Response > 75%	7 (35%)	2 (10%)	
Seizure Free	1 (5%)	4 (20%)	
Subjective Change at Follow-Up (patient report)			
Mean Reduction in 'Small Seizures' per Month (median)	40.7% (50.0)	54.7% (50.0)	*P* = .25
Mean Reduction in 'Big Seizures' per Month (median)	29.4% (50.0)	38.3% (80.0)	*P* = .11
Mean Reduction in Total Seizures per Month (median)	43.8% (47.7)	53.5% (50.0)	*P* = .64
Seizures Worsened	0	0	
Seizures Unchanged	10 (50%)	9 (45%)	
Response > 50%	8 (40%)	6 (30%)	*P* = .54
Good Response > 75%	1 (5%)	1 (5%)	
Seizure Free	1 (5%)	4 (20%)	
Change in Maximum Interval of Seizure-Free Days (if not seizure free) (SD)	105.6% (50.0)	160.0% (42.9)	*P* = .47
Seizure Frequency Change Rating	1.2 (2.4)	1.8 (2.3)	*P* = .31
Impact on Seizures On Quality of Life			
Bodily Well-being	2.1 (1.4)	1.9 (1.4)	*P* = .55
Bodily Performance	2.4 (1.7)	1.8 (1.5)	*P* = .14
Cognitive Performance	2.1 (1.8)	1.8 (1.5)	*P* = .70

Outcome	VNS N = 20	AED N = 20	P Value
Emotional Well-being	2.4 (1.7)	2.9 (1.8)	*P* = .48
Change in AED Treatment			
Mean Number of AEDs (SD)	2.47 (0.77)	2.24 (0.44)	*P* = .03

Note. Seizure severity outcome not reported as not measured using a validated scale. Abbreviations. AED: antiepileptic drug; SD: standard deviation; VNS: vagal nerve stimulation

Table C20. Adverse Events at Each Time Point (Kawai et al., 2017[68])

Adverse Event	At Implantation	At Stimulation Start	At 3 Months	At 6 Months	At 12 Months	At 24 Months	At 36 Months
Laryngeal Symptoms, Including Hoarseness and Coughing	36 (9.7%)	41 (11.2%)	28 (7.7%)	20 (5.6%)	9 (2.5%)	16 (4.6%)	15 (4.5%)
Local Dysesthesia	4 (1.1%)	6 (1.6%)	0	4 (1.1%)	2 (0.6%)	1 (0.3%)	1 (0.3%)
Cardiac Complications, Including Asystole and Bradycardia	7 (1.9%)	0	0	0	1 (0.3%)	0	0
Respiratory Complications	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Local Infection	0	1 (0.3%)	2 (0.6%)	0	2 (0.6%)	0	1 (0.3%)
High Lead Impedance	0	1 (0.3%)	1 (0.3%)	2 (0.6%)	3 (0.8%)	3 (0.8%)	10 (3.0%)
Others	2 (0.5%)	0	4 (1.1%)	2 (0.6%)	3 (0.8%)	6 (1.7%)	2 (0.6%)

Table C21. Adverse Events at Each Time Point (Kawai et al., 2017[68])

Adverse Event	At Implantation	At Stimulation Start	At 3 Months	At 6 Months	At 12 Months	At 24 Months	At 36 Months	At Any Time During Follow-Up
Voice Change/Hoarseness	17	15	19	11	2	7	9	58
Coughing	13	21	5	7	5	4	3	50
High Lead Impedance	0	1	1	2	3	3	10	19
Dysphagia	6	4	3	1	0	1	1	16
Death	0	0	1	0	3	5	5	14
Local Pain	4	2	0	2	1	1	1	11
Local Paresis	0	3	0	2	1	0	0	6
Local Infection	0	1	2	0	2	0	1	6
Dyspnea	0	1	0	0	1	1	1	4
Cardiac Dysrhythmia	3	0	0	0	1	0	0	4
Seizure	0	3	1	0	0	0	0	4
Hiccupping	0	0	0	1	1	0	1	3
Bradycardia	3	0	0	0	0	0	0	3
Aspiration Pneumonia	0	1	0	0	0	0	1	2
Vertigo	0	0	1	0	0	1	0	2
Bronchitis/Lower Respiratory Infection	0	0	0	0	1	0	1	2
Salivation	0	0	1	0	0	1	0	2
Asystole	1	0	0	0	0	0	0	1
Discomfort	1	0	0	0	0	0	0	1
Right Femoral Head Fracture	0	0	0	0	0	0	1	1
Agitation	0	0	0	0	0	1	0	1
Myoclony	0	0	0	0	1	0	0	1
Weight Loss	0	0	0	1	0	0	0	1
Nausea	0	0	0	0	0	1	0	1
Local Irritation	0	1	0	0	0	0	0	1
Restlessness	0	0	1	0	0	0	0	1
Fever	1	0	0	0	0	0	0	1
Chest Pain	0	0	0	1	0	0	0	1
Belching	0	0	1	0	0	0	0	1
Muscle Spasm	0	0	0	0	1	0	0	1

Adverse Event	At Implantation	At Stimulation Start	At 3 Months	At 6 Months	At 12 Months	At 24 Months	At 36 Months	At Any Time During Follow-Up
Incontinence	0	0	0	0	0	0	1	1
Violent Behavior	0	0	0	0	0	1	0	1
Early Battery Depletion	0	0	0	0	1	0	0	1
Shortness of Breath	0	0	0	0	0	1	0	1
Facial Pallor	0	0	0	0	1	0	0	1
Decreased Oxygen Desaturation	0	0	0	1	0	0	0	1
Dry Vomiting	0	0	0	0	0	1	0	1
Nausea	0	0	1	0	0	0	0	1
Wheezing	0	0	0	0	0	1	0	1
Acute Pancreatitis	0	0	0	0	0	1	0	1
Vocal Cord Cordopexy (paralysis)	0	0	0	0	0	1	0	1

Note. Nausea is reported twice in the published supplementary appendix. It is not clear why this duplication.

Table C22. Seizure Frequency by Treatment Group and Seizure Type (Kuba et al., 2013[69])

Outcome	Number of Seizures per Month					
	Baseline		At 2 years		At 5 Years	
	VNS	Surgery	VNS	Surgery	VNS	Surgery
All Seizure Types						
Range	3 to 220	8 to 400	0 to 130	0 to 150	0 to 150	0 to 130
Mean (SD)	58.4 (62.1)	78.8 (94.9)	28.7 (40.1)	26.3 (43.5)	27.4 (42.3)	22.6 (32.7)
Median	40	30	10	4.5	5	4
Within Group Difference From Baseline	NA	NA	*P* < .001	*P* < .001	*P* < .001	*P* < .001
Between Group Difference	NA	NA	*P* = .22		*P* = .22	
Focal Seizures						
Range	2 to 220	12 to 400	0 to 130	0 to 150	0 to 150	0 to 130
Mean (SD)	65.5 (63.6)	82.7 (92.6)	32.1 (42.2)	27.7 (44.3)	30.9 (40.6)	24.3 (39.6)
Median	40	35	10	5	10	5
Within Group Difference From Baseline	NA	NA	*P* < .001	*P* < .001	*P* < .001	*P* < .001
Secondary Generalized Tonic–clonic Seizures						
Range	1 to 10	1 to 25	0 to 10	0 to 5	0 to 10	0 to 5
Mean (SD)	4.35 (2.9)	5.75 (7.0)	2.3 (2.7)	1.8 (2.0)	1.9 (2.7)	2.1 (2.1)
Median	3	3	1	2	1	2
Within Group Difference From Baseline	NA	NA	*P* < .001	*P* < .001	*P* < .001	*P* < .001

Note. We have assumed the data are mean and SD, where appropriate, but this was not explicitly stated in the paper. The data are as reported in the text, rather than the table; there are differences. Abbreviations. NA: not applicable; SD: standard deviation; VNS: vagal nerve stimulation.

Table C23. Engel and McHugh Classification by Treatment Group and Seizure Type (Kuba et al., 2013[69])

Classification	VNS	Surgery	*P* Value
At 2 Years			
Engel I (free of disabling seizures)	5.8%	23.1%	*P* = .04
Engel II (rare disabling seizures)	8.6%	23.1%	*P* = .007[a]
Engel III (worthwhile improvement)	43.3%	19.2%	NR
Engel IV (no worthwhile improvement)	43.3%	34.6%	NR
McHugh I (80 to 100% seizure reduction)	20.0%	50.0%	*P* = .009
McHugh II (50 to 79% seizure reduction)	28.5%	12.0%	*P* = .09[b]
McHugh III (< 50% seizure reduction)	34.3%	8.0%	NR
McHugh II (magnet benefit only)	2.8%	0	NR

Classification	VNS	Surgery	*P* Value
McHugh II (no improvement)	14.4%	30.0%	NR
At 5 Years			
Engel I (free of disabling seizures)	7.9%	36.8%	*P* = .01
Engel II (rare disabling seizures)	17.2%	10.5%	*P* = .02[a]
Engel III (worthwhile improvement)	44.8%	21.0%	NR
Engel IV (no worthwhile improvement)	31.1%	31.7%	NR
McHugh I (80 to 100% seizure reduction)	34.5%	52.6%	*P* = .04
McHugh II (50 to 79% seizure reduction)	34.5%	5.3%	*P* = .34[b]
McHugh III (< 50% seizure reduction)	15.5%	15.8%	NR
McHugh II (magnet benefit only)	0	0	NR
McHugh II (no improvement)	15.5%	26.3%	NR

Note. [a] Combined Engel I and II; [b] Combined McHugh I and II. Abbreviations. NR: not reported; VNS: vagal nerve stimulation.

Table C24. Rates of SUDEP (Ryvlin et al., 2018[75])

Group	Crude SUDEP Rater per 1,000 Person-Years				Age-Adjusted SUDEP Rater per 1,000 Person-Years			
	Trend Test	Years 1 to 2	Years 3 to 10	Rate Ratio (95% CI)	Trend Test	Years 1 to 2	Years 3 to 10	Rate Ratio (95% CI)
Adjudication Per Protocol								
All Ages N = 632	*P* =.008	2.74	2.10	0.77 0.65 to 0.91)	*P* = .008	2.47	1.68	0.68 (0.53 to 0.87)
Ages 10 to 54 N = 560	*P* < .001	3.02	2.19	0.73 (0.61 to 0.87)	*P* < .001	3.00	2.16	0.72 (0.64 to 0.81)
Probable and Definite SUDEP								
All Ages N = 101	*P* < .001	0.67	0.25	0.37 (0.25 to 0.55)	*P* < .001	0.56	0.19	0.34 (0.23 to 0.51)
Ages 10 to 54 N = 89	*P* < .001	0.67	0.28	0.41 (0.27 to 0.62)	*P* < .001	0.67	0.27	0.41 (0.31 to 0.54)

Note. Results are from the per-protocol analysis. Abbreviations. CI: confidence interval; SUDEP: sudden unexpected death in epilepsy.

Table C25. Quality of Life Outcomes for Children with Refractory Epilepsy (Sherman et al., 2008[76])

Quality of Life Measure	Timing	VNS	Standard Medical Treatment	P Value
		Mean (SD)	Mean (SD)	
Epilepsy-specific	Baseline	22.6 (7.3)	11.1 (8.5)	*P* < .001
	Retest	19.8 (8.8)	14.1 (8.3)	Not reported
Global	Baseline	3.5 (1.4)	4.4 (1.5)	*P* = .04
	Retest	3.6 (1.3)	4.4 (1.2)	Not reported

Note. Higher epilepsy specific scores indicate worse quality of life. Higher global ratings indicate better quality of life. Abbreviations. SD: standard deviation; VNS: vagal nerve stimulation.

Table C26. Changes in Quality of Life for Children with Refractory Epilepsy (Sherman et al., 2008[76])

Changes in Quality of Life	VNS	Standard Medical Treatment	*P* Value
Epilepsy-specific			
Worsened	14%	37%	*P* = .07
Unchanged	52%	53%	Not reported (assumed nonsignificant)
Improved	33%	11%	*P* > .05
Global			
Worsened	9%	11%	Not reported (assumed nonsignificant)
Unchanged	77%	83%	*P* > .05
Improved	14%	6%	Not reported (assumed nonsignificant)

Abbreviation. VNS: vagal nerve stimulation.

Table C27. Subgroup Analyses (Aaronson et al., 2017[56])

Outcome	VNS+TAU	TAU	*P* Value
Responders to Previous Adequate ECT (defined as at least 7 right unilateral treatments)			
Cumulative Response Rate at 5 Years, Based on MADRS Score	71.3% (95% CI, 64.3% to 77.4%)	56.9% (95% CI, 44.8% to 68.2%)	*P* = .006
Nonresponders to Previous Adequate ECT (defined as at least 7 right unilateral treatments)			
Cumulative Response Rate at 5 Years, Based on MADRS Score	59.6% (95% CI, 50.2% to 68.4%)	34.1% (95% CI, 21.8% to 48.9%)	*P* < .001

Abbreviations. CI: confidence interval; ECT: electroconvulsive therapy; MADRS: Montgomery-Åsberg Depression Rating Scale; TAU: treatment as usual; VNS: vagal nerve stimulation.

Table C28. Kaplan-Meier Probability Estimates for Response and Duration of Response (Kumar et al., 2019[70])

Treatment Group	3 Months	6 Months	9 Months	12 Months
Probability of First Response Over Time (95% CI)				
TNS	0 (0 to .03)	.10 (.07 to .15)	.19 (.15 to .24)	.24 (.19 to .30)
VNS+TAU	.01 (0 to .03)	.22 (.17 to .27)	.33 (.28 to .38)	.42 (.36 to .47)
Probability of Retaining the First Response (Response Durability)Over Time (95% CI)				
TNS	.75 (.63 to .84)	.58 (.45 to .69)	.41 (.29 to .53)	.39 (.27 to .51)
VNS+TAU	.85 (.78 to .90)	.65 (.57 to .73)	.52 (.43 to .60)	.47 (.38 to .56)
Probability of Second Response Over Time Following Relapse From the First Response (95% CI)				
TNS	0	.13 (.06 to .27)	.27 (.16 to .43)	.32 (.20 to .48)
VNS+TAU	.07 (.04 to .15)	.26 (.18 to .36)	.44 (.35 to .55)	.47 (.37 to .58)
Probability of Retaining Second Response (Response Durability) Over Time (95% CI)				
TNS	.97 (.79 to 1.00)	.82 (.63 to .92)	.63 (.42 to .78)	.46 (.27 to .64)
VNS+TAU	.98 (.89 to 1.00)	.89 (.78 to .95)	.73 (.59 to .82)	.66 (.52 to .77)

Abbreviations. CI: confidence interval; TAU: treatment as usual; VNS: vagal nerve stimulation.

Table C29. Mortality by Treatment Group (Feldman et al., 2013[61])

Mortality per 1,000 Patient Years (95% CI)	VNS Years 1 and 2 Post Implantation	TRD Years 1 and 2 Post Identification	Managed Depression Years 1 and 2 Post Identification	P Value for VNS Compared With Other Groups
Overall	19.9	46.2 (41.9 to 50.6)	46.8 (43.4 to 50.4)	*P* < .001
Under 40 Years	25.4	12.5 (7.0 to 19.1)	15.1 (9.1 to 21.8)	*P* > .05
40 to 64 Years	10.3	25.8 (20.9 to 30.9)	24.6 (20.8 to 28.5)	*P* < .001
65 Years and Older	52.0	81.4 (72.8 to 90.2)	77.0 (70.5 to 83.5)	*P* < .001

Abbreviations. CI: confidence interval; TRD: treatment-resistant depression; VNS: vagal nerve stimulation.

Table C30. Depression Severity Over Time (George et al., 2005[62])

Time Point	Model-Estimated Differences (SE) between VNS+TAU and TAU, Measured by the IDS-SR	P Value
3 months	-1.19 (0.29)	Not reported
6 months	-2.38 (0.58)	
9 months	-3.57 (0.87)	
12 months	-4.76 (1.16)	

Abbreviations. IDS-SR: Inventory of Depressive Symptomatology - Self Report; SE: standard error; TAU: treatment as usual; VNS: vagal nerve stimulation.

Table C31. Depression Severity Over Time (George et al., 2005[62])

Outcome	VNS+TAU	TAU	*P* Value
IDS-SR$_{30}$ Score			
Baseline mean score (SD)	42.9 (10.0)	43.8 (10.5)	*P* = .91
12 month score			
OC average change (SD)	-9.8 (13.2)	-4.6 (12.6)	*P* < .001
OC average change (SD) (adjusted mean)	-9.9 (1.0)	-3.7 (1.3)	*P* < .001
LOCF average change (SD)	-9.3 (13.4)	-5.0 (12.6)	*P* < .001
LOCF average change (SD) (adjusted mean)	-9.3 (1.0)	-4.2 (1.2)	*P* < .001
OC response rates	21.7%	11.6%	*P* = .03
LOCF response rates	19.6%	12.1%	*P* = .11
OC remission rates	15.0%	3.6%	*P* = .006
LOCF remission rates	13.2%	3.2%	*P* = .007
OC sustained response	15.5%	4.6%	*P* = .005
HRSD$_{24}$ Score			
Baseline mean score (SD)	28.0 (5.7)	27.5 (5.1)	*P* = .96
12 month score			
OC average change (SD)	-8.2 (9.1)	-4.9 (7.8)	*P* = .006
OC average change (SD) (adjusted mean)	-8.3 (0.7)	-5.1 (0.9)	*P* = .006
LOCF average change (SD)	-7.4 (9.4)	-4.9 (7.8)	*P* = .04
LOCF average change (SD) (adjusted mean)	-7.4 (0.6)	-5.0 (0.9)	*P* = .04
OC response rates	29.8%	12.5%	*P* = .003
LOCF response rates	26.8%	12.5%	*P* = .01
OC complete response rates	17.1%	6.7%	*P* = .03
LOCF complete response rates	15.6%	6.7%	*P* = .06
CGI-I Score			
12 month data			
OC Much or Very Much Improved	36.5%	11.9%	*P* < .001
LOCF Much or Very Much Improved	34.0%	11.9%	*P* < .001

Abbreviations. CGI-I: Clinical Global Impression – Improvement; HRSD; Hamilton Rating Scale Depression; IDS-SR: Inventory of Depressive Symptomatology Self Report; LOCF: last observation carried forward; OC: observed case; SD: standard deviation; TAU: treatment as usual; VNS: vagal nerve stimulation.

Table C32. Study Characteristics and Evidence Tables for Economic Studies

Citation Country	Design Test Comparator(s)	Population Analytic Assumptions	Main Findings
Epilepsy			
Fallah et al., 2016[88] U.S.	Aim: To evaluate the cost-utility of 4 competing antiseizure treatment strategies for children with focal drug-resistant epilepsy secondary to Tuberous Sclerosis Complex that is amenable to surgery Design: Cost-utility analysis (Monte Carlo simulation) Intervention: VNS Comparators: • Resective surgery • Ketogenic diet • mTOR inhibitor • Addition of another AED	Population: Hypothetical cohort of children • Under 18 years of age • Treated at a tertiary care hospital • Seizures that did not improve from treatment with 2 first-line AEDs (valproic acid and levetiracetam) A secondary analysis evaluated the same cohort of children with seizures refractory to 3 first-line AEDs; the analysis additionally included a fourth AED (clobazam) and a fifth treatment (everolimus) Conditions: Drug-resistant epilepsy secondary to Tuberous Sclerosis Complex amenable to surgery Analytic assumptions: • Perspective of a third-party payer • Time horizon of 5 years • Costs included direct health care costs of therapy, subsequent hospitalizations, and AED treatment • Annual discount rate of 3% • Costs in 2016 U.S. dollars, with historic costs adjusted to present value • Costs for physician services and procedures were taken from a combination of a literature review of MEDLINE, 2016 American Medical	See Tables C36 and C37 for cost-effectiveness results In the primary analysis, sensitivity analysis identified variables that affected cost-effectiveness, but not the dominance of treatment strategies See Table C38 for sensitivity analysis for the secondary analysis For children who have failed 2 AEDS, the addition of a third AED remained the most cost-effective strategy in probability sensitivity analysis When willingness-to-pay is less than $184,000 per additional QALY, the addition of a third AED is the most cost-effective treatment strategy every time When willingness-to-pay is greater than $420,000 per additional QALY, resective surgery is the most cost-effective treatment strategy As the willingness-to-pay increases between $184,000 and $420,000 per additional QALY, resective surgery gradually becomes the more cost-effective option For children who have failed 3 AEDS, the cost-utility acceptability curve found a threshold for willingness-to-pay of $67,500 over which the addition of a fourth AED becomes more cost-effective than the ketogenic diet A second threshold for willingness-to-pay is of $97,000 over which resective surgery becomes

Citation Country	Design Test Comparator(s)	Population Analytic Assumptions	Main Findings
		Association Current Procedural Terminology codebook, ICD-9-CM codes, and Medical Expenditure Panel • Microcosting used for AEDs, based on drug costs from an discounted online website • Survey [20], Agency for Healthcare Research and Quality Website • Willingness-to-pay was set at $100,000 per QALY • Full medical adherence • Rate of adverse events: 0% • Rate of major complications or death: 0% • Rate of crossovers: 0% • Rate of AED withdrawal: 0% • Seizure outcome after surgery at 1 year remained the same over the 5 years • VNS battery change occurs once over the 5 years • Ketogenic diet is followed for only 2 years • Rate of seizure freedom continuing, after termination of the ketogenic diet: 80% • If the third AED is not effective, the child remains on all 3 AEDs and continues to have seizures • Multiple one-way sensitivity analyses and probability sensitivity analysis See Tables C33 to C35 for base-case estimates, outcome probabilities, and health state utilities	more cost-effective than the addition of a fourth ASD When willingness-to-pay is between $67,500 and $97,000, the addition of a fourth AED is more commonly the cost-effective treatment strategy There is no cost for VNS implantation or mTOR inhibitor that would make these treatment strategies more cost-effective than the addition of a third ASD (these strategies are more costly and less effective than alternative strategies and, therefore, dominated) in children who had failed 2 AEDs For children who had failed 3 AEDs, the cost of the mTOR inhibitor would have to be less than $800 per year to be a cost-effective treatment strategy. Assuming that the cost of a battery replacement was one-quarter the cost of a new VNS implantation, two-way sensitivity analysis showed that a cost combination of $7000 and $1750 or lower for VNS implantation and battery replacement, respectively, would make this treatment strategy cost-effective compared with the alternatives

Citation Country	Design Test Comparator(s)	Population Analytic Assumptions	Main Findings
Purser et al., 2018[89] U.S.	Aim: To estimate, from the perspective of a managed care organization, the budget impact and effect on health outcomes of expanded use of VNS among patients aged 12 and older with drug-resistant epilepsy with partial-onset seizures Design: Budget impact model Intervention: VNS Comparator: No VNS	Population: Theoretical cohort of patients • Aged 12 or older • With drug-resistant partial-onset seizures • Not currently with VNS Of 1,000,000 members, an estimated 1,536 (0.15%) would meet these criteria Conditions: Drug-resistant epilepsy with partial-onset seizures Analytic assumptions: • Perspective of a U.S. managed care organization • Time horizon of 5 years • Costs in 2016 U.S. dollars, with historic costs adjusted to present value • Annual discount rate not reported • All patients started with 10 or more seizures per month • No further changes in seizure frequency occur after 24 months See Tables C39 to C41 for model assumptions and resource utilization inputs	See Table C42 for budget impact results Initial VNS device, placement, and programming costs were offset in 1.7 years after implantation On average, VNS resulted in an estimated net cost savings of $77,480 per patient over 5 years, a 21.5% reduction in costs compared with AEDs alone Patients with VNS had an estimated reduction in costs associated with seizure frequency of $127,554 per patient over 5 years compared with patients with AEDs alone Seizure-related hospitalizations were the main cost driver, resulting in an estimated cost reduction of $118,925 per patient over 5 years for patients with VNS compared with AEDs alone Results were most sensitive to per-person hospitalization cost per year with and without VNS in years 3 to 5 after VNS device placement; however, VNS remained cost saving over 5 years If the proportion of patients who became seizure-free at 24 months was raised from 8% to 15.4%, the cost reduction over 5 years was 22.5% compared with AEDs alone If the proportion of patients having 10 or more seizures at 3 months who moved to fewer than 10 seizures at 24 months was raised from 20% to 42%, the cost reduction over 5 years was 28.9% compared with AEDs alone, with a break-even point of 1.54 years

Abbreviations. AED: antiepileptic drug; ASD: autism spectrum disorder; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; mTOR: mammalian target of rapamycin; QALY: quality-adjusted life year; VNS: vagal nerve stimulation.

Table C33. Base-Case Estimates of Costs, Updated to 2016 U.S. Dollars (Fallah et al., 2016[88])

Parameter	Best Base-case Estimate	Range in the Literature	Range Tested in Sensitivity Analysis
Cost Of Levetiracetam	$96.00	$72.72 to $390.31	$69.08 to $409.83
Cost Of Valproic Acid	$645.49	$259.82 to $647.27	$246.83 to $679.63
Cost Of Resective Surgery	$46,778.00	$24,449.00 to $49,871.51	$23,226.55 to $52,365.09
Evaluation Cost — Resective Surgery	$12,355.39	$9,982.31 to $14,728.46	$9,483.19 to $15,464.89
Cost Of VNS Insertion	$17,938.31	$8,295.87 to $17,938.31	$7,881.08 to $18,835.22
Cost Of VNS Battery Replacement	$7,994.25	NA	$7,594.54 to $8,393.96
Evaluation Cost — No Resective Surgery	$8,135.00	$6,287.69 to $9,982.31	$5,973.31 to 10,481.43
Follow-Up Costs Following Surgical Treatment — First 2 Years	$4,783.85	NA	$4,544.66 to $5,023.04
Cost of mTOR	$134,436.00	$150,249.16 to $152,821.24	$142,736.70 to $160,462.30
Cost of Ketogenic Diet — Initiation	$4,824.43	NA	$4,583.21 to $5,065.65
Cost Of Ketogenic Diet — Ongoing	$2,737.50	NA	$2,600.63 to $2,874.38
Cost Of Third AED (carbamazepine)	$52.00	$52.00 to $1,662.24	$49.40 to $1,745.35
Cost Of Fourth AED (clobazam)	$9,301.38	$9,301.38 to $9,792.00	$8,836.31 to $10,281.60
Follow-Up Costs Following Medical Treatment — First 2 Years	$3,560.77	NA	$3,382.73 to $3,738.81
Follow-Up Hospitalization Costs Following Surgical Treatment — After 2 Years (seizure-free)	$0.00	NA	NA
Follow-Up Hospitalization Costs Following Surgical Treatment — After 2 Years (reduction in seizures)	$593.08	NA	$563.43 to $622.73
Follow-Up Hospitalization Costs Following Surgical Treatment — After 2 Years (no response)	$2,280.00	NA	$2,166.00 to $2,394.00

Abbreviations. AED: antiepileptic drug; mTOR: mammalian target of rapamycin; NA: not applicable; VNS: vagal nerve stimulation.

Table C34. Outcome Probabilities (Fallah et al., 2016[88])

Outcome	Probability	Range in the Literature	Range Tested in Sensitivity Analysis
Resective Surgery			
Engel Class I	.55	.50 to .65	.45 to .70
Engel Class II	.13	.13 to .18	.08 to .23
Engel Class III	.15	.12 to .25	.07 to .30
VNS Implantation			
Engel Class I	.12	.05 to .19	.00 to .24
Engel Class II	.11	.08 to .31	.03 to .36
Engel Class III	.42	.13 to .64	.08 to .71
Ketogenic Diet			
Engel Class I	.00	.00 to .11	.00 to .16
Engel Class II	.07	.07 to .35	.02 to .40
Engel Class III	.32	.10 to .32	.05 to .37
mTOR Inhibitor			
Engel Class I	.20	.00 to .20	.00 to .25
Engel Class II	.35	.00 to .35	.00 to .40
Engel Class III	.05	.05 to .57	.00 to .62
Third AED (carbamazepine)			
Seizure Free	.06	NA	.01 to .11

Abbreviations. AED: antiepileptic drug; mTOR: mammalian target of rapamycin; NA: not applicable; VNS: vagal nerve stimulation.

Table C35. Health State Utilities of Treatment Outcomes (Fallah et al., 2016[88])

Outcome	Probability	Range in the Literature	Range Tested in Sensitivity Analysis
Seizure-free State (nonsurgical treatment)	.94	NA	.92 to .96
No Change in Seizure Frequency (nonsurgical treatment)	.84	NA	.82 to .86
Less than 50% Reduction in Seizure Frequency (nonsurgical treatment)	.82	NA	.80 to .84
Engel Class I	.96	NA	.94 to .98
Engel Class II	.91	NA	.89 to .93
Engel Class III	.79	NA	.77 to .81
Engel Class IV	.66	NA	.64 to .68

Note. A perfect health state utility is defined as 1. Abbreviation. NA: not applicable.

Table C36. Cost-effectiveness Results for the Primary Analysis (Fallah et al., 2016[88])

Treatment Strategy	5 Year Total Cost	Incremental Cost[a]	5 Year Total Utility (QALY)	Incremental Utility (QALY)[a]	Incremental Cost-effectiveness Ratio[b]
Third AED (carbamazepine)	$6,568.49	NA	4.14	NA	NA
Ketogenic Diet	$13,458.85	$6,890.36	3.60	-0.54	Dominated[c]
VNS Implantation	$50,742.96	$44,174.47	3.89	-0.25	Dominated[c]
Resective Surgery	$73,383.93	$66,815.44	4.38	0.25	$268,335.11/QALY

Note. [a] Incremental cost and utility represent the difference between the strategy and the next best nondominated strategy; [b] Incremental cost/utility ratio represents the difference in cost divided by the difference in QALYs for each strategy compared with the next best nondominated strategy. The cost and QALY values are rounded in the calculations; [c] Strategies that are dominated are more costly and less effective than alternative treatment strategies. Abbreviations. AED: antiepileptic drug; NA: not applicable; QALY: quality-adjusted life year; VNS: vagal nerve stimulation.

Table C37. Cost-effectiveness Results for the Secondary Analysis (Fallah et al., 2016[88])

Treatment Strategy	5 Year Total Cost	Incremental Cost[a]	5 Year Total Utility (QALY)	Incremental Utility (QALY)[a]	Incremental Cost-effectiveness Ratio[b]
Ketogenic Diet	$16,227.58	NA	3.60	NA	NA
Fourth AED (clobazam)	$50,861.83	$34,634.25	4.11	0.51	$67,579.03/QALY
VNS Implantation	$53,511.68	$37,284.10	3.89	0.30	Dominated[c]
Resective Surgery	$77,675.46	$61,447.88	4.38	0.79	$77,831.39/QALY
mTOR Inhibitor (everolimus)	$646,045.93	$629,818.35	4.07	0.47	Dominated[c]

Note. [a] Incremental cost and utility represent the difference between the strategy and the next best nondominated strategy; [b] Incremental cost/utility ratio represents the difference in cost divided by the difference in QALYs for each strategy compared with the next best nondominated strategy. The cost and QALY values are rounded in the calculations; [c] Strategies that are dominated are more costly and less effective than alternative treatment strategies. Abbreviations. AED: antiepileptic drug; mTOR: mammalian target of rapamycin; NA: not applicable; QALY: quality-adjusted life year; VNS: vagal nerve stimulation.

Table C38. Sensitivity Analysis for the 5 Treatment Strategies (Fallah et al., 2016[88])

Parameter	Base-case Estimate	Threshold	Comment
Cost Of Resective Surgery Year 1	$46,778.00	$60,019.76	If cost exceeds this threshold, then the addition of a fourth AED (clobazam) is more cost-effective than resective surgery
Probability Of Engel Class I Seizure Outcome With Resective Surgery	.55	.54	If probability falls below this threshold, then the addition of a fourth AED (clobazam) is more cost-effective than resective surgery
Probability Of Engel Class II Seizure Outcome With Resective Surgery	.13	.12	If probability falls below this threshold, then the addition of a fourth AED (clobazam) is more cost-effective than resective surgery
Probability Of Engel Class III Seizure Outcome With Resective Surgery	.15	.14	If probability falls below this threshold, then the addition of a fourth AED (clobazam) is more cost-effective than resective surgery
Probability Of Engel Class II Seizure Outcome With VNS Implantation	.11	.31	If probability exceeds this threshold, then VNS implantation is more cost-effective than resective surgery
Probability Of Engel Class I Seizure Outcome With Ketogenic Diet	.00	.12	If probability exceeds this threshold, then ketogenic diet is more cost-effective than resective surgery
Probability Of Engel Class II Seizure Outcome With Ketogenic Diet	.07	.21	If probability exceeds this threshold, then ketogenic diet is more cost-effective than resective surgery
Utility Of Engel Class I Seizure Outcome	.96	.956	If utility falls below this threshold, then the addition of a fourth AED (clobazam) is more cost-effective than resective surgery
Utility Of Engel Class II Seizure Outcome	.91	.896	If utility falls below this threshold, then the addition of a fourth AED (clobazam) is more cost-effective than resective surgery
Utility Of Engel Class III Seizure Outcome	.79	.778	If utility falls below this threshold, then the addition of a fourth ASD (clobazam) is more cost-effective than resective surgery
Utility Of Engel Class IV Seizure Outcome	.66	.650	If utility falls below this threshold, then the addition of a fourth ASD (clobazam) is more cost-effective than resective surgery
Utility Of Less Than 50% Reduction In Seizure Frequency	.82	.822	If probability exceeds this threshold, then the addition of a fourth ASD (clobazam) is more cost-effective than resective surgery

Abbreviation. AED: antiepileptic drug; ASD: autism spectrum disorder; VNS: vagal nerve stimulation.

Table C39. Model Inputs by Treatment Group (Purser et al., 2018[89])

Parameter	Costs per Person With VNS	Costs per Person Without VNS
VNS Device Related Costs		
VNS Device (generator, lead, tunneler)	$36,239	NA
Procedure for Full System Placement	$2,661	NA
Neurologist Visits for Programming	$319	NA
Battery Replacement (per person per year)	$2,178	NA
VNS Adverse Event Costs		
Neurologist Visit for Cough	$40	$0
Neurologist Visit for Cough (voice alteration)	$42	$0
Surgical Site Infection Resulting in VNS Removal	$95	NA
AED Costs		
AED Costs per Year	$6,502	$6,502

Abbreviations. AED: antiepileptic drug; NA: not applicable; VNS: vagal nerve stimulation.

Table C40. Resource Use by Seizure Frequency (Purser et al., 2018[89])

Resource	Unit Cost	Seizure Free		≤ 1 Seizure per Month		> 1 to < 10 Seizures per Month		≥ 10 Seizures per Month	
		Number of Episodes	Costs per Person Per Year	Number of Episodes	Costs per Person Per Year	Number of Episodes	Costs per Person Per Year	Number of Episodes	Costs per Person Per Year
Hospitalization	$12,360	0	$0	0.48	$5,933	0.96	$11,866	4.8	$59,330
ED Visits	$1,079	0	$0	0.42	$453	0.85	$917	3.57	$3,852
Neurologist Visits	$106	16.62	$1,769	17.37	$1,849	18.12	$1,929	22.54	$2,399
Total Cost		**$1,769**		**$8,235**		**$14,712**		**$65,581**	

Abbreviations. AED: antiepileptic drug; ED: emergency department; NA: not applicable; VNS: vagal nerve stimulation.

Table C41. Costs Inputs of Resource Use by Treatment Group (Purser et al., 2018[89])

Resource	Year 1		Year 2		Year 3 to 5	
	With VNS	Without VNS	With VNS	Without VNS	With VNS	Without VNS
Hospitalization	$38,737	$59,330	$34,954	$59,330	$33,563	$59,330
ED Visits	$2,571	$3,852	$2,329	$3,852	$2,238	$3,852
Neurologist Visits	$2,193	$2,399	$2,154	$2,399	$2,139	$2,399
Total	$43,501	$65,581	$39,437	$65,581	$37,913	$65,581

Abbreviations. ED: emergency department; VNS: vagal nerve stimulation.

Table C42. Budget Impact by Treatment Group (Purser et al., 2018[89])

Outcome	Year 1	Year 2	Year 3 to 5 per Year	Total of Years 1 to 5
Cost Without VNS	$110,709,545	$110,709,545	$110,709,545	$553,547,724
Cost With VNS	$141,644,874	$74,932,599	$72,657,493	$434,549,953
Budget Impact	$30,935,329	($35,776,946)	($38,052,052)	($118,997,771)
Relative Difference	27.94%	-32.32%	-34.37%	-21.5%

Note. Brackets indicate a cost saving. Abbreviation. VNS: vagal nerve stimulation.

Appendix D. Risk of Bias Assessments

Table D1. Risk of Bias: Randomized Controlled Trials

Study	Randomization	Allocation Concealment	Intervention	Outcomes	Investigator & Participant Masking	Outcome Assessor Masking	Intention to Treat Analysis	Statistical Analysis	Other Biases	Interest Disclosure	Funding	Overall Risk of Bias Assessment Comments
Aaronson et al., 2013[78]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No other major biases noted	No	No	**Moderate** Some concern about conflicts of interest and industry funding
Bauer et al., 2016[79]	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	No	No other major biases noted	No	No	**High** Serious concern about lack of reporting of methods, high loss to follow-up, and conflicts of interest not reported
Handforth et al., 1998[80] Dodrill et al., 2001[49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No other major biases noted	No	No	**Moderate** Some concern about industry funding and author conflicts of interest
Hein et al., 2013[81]	Unclear	Unclear	Yes	No	Unclear	Unclear	Unclear	Unclear	Small sample sizes	Yes	No	**High** Serious concern about the lack of

Study	Randomization	Allocation Concealment	Intervention	Outcomes	Investigator & Participant Masking	Outcome Assessor Masking	Intention to Treat Analysis	Statistical Analysis	Other Biases	Interest Disclosure	Funding	Overall Risk of Bias Assessment Comments
												reporting of methods, small sample sizes, and conflicts of interest not reported
Klinkenberg et al., 2012[82] Klinkenberg et al., 2013[83]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No other major biases noted	No	No	**Moderate** Some concern about allocation concealment, the lack of reporting of analysis, interests and funding
Landy et al., 1993[51]	No	No	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Small sample sizes	Yes	No	**High** Serious concern about the lack of reporting of methods, small sample sizes, and industry sponsored
Rush et al., 2005[85] Nierenberg et al., 2008[84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No other major biases noted	No	No	**Moderate** Some concern about randomization and industry funding

Study	Randomization	Allocation Concealment	Intervention	Outcomes	Investigator & Participant Masking	Outcome Assessor Masking	Intention to Treat Analysis	Statistical Analysis	Other Biases	Interest Disclosure	Funding	Overall Risk of Bias Assessment Comments
Ryvlin et al., 2014[86]	Yes	Yes	Yes	Yes	No	No	No	No	Study terminated early	No	No	**High** Serious concern about lack of blinding, early termination, and industry involvement
Vagus Nerve Stimulation Group, 1995[87] Elger et al., 2000[50]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Major protocol violations noted	No	No	**High** Some concern about industry funding and major protocol violations

Table D2. Risk of Bias: Nonrandomized Studies

Study	Participant Selection	Intervention Exposure	Appropriate Comparator	Outcomes	Outcome Assessor Masking	Confounding	Statistical Analysis	Other Biases	Interest Disclosure	Funding	Overall Risk of Bias Assessment Comments
Aaronson et al., 2017[56] Conway et al., 2018 [59] Kumar et al., 2019[70]	Yes	Yes	Yes	Yes	No	Yes	Unclear	No other major biases noted	No	No	**Moderate** Some concern about conflicts of interest
Amar et al., 2004[57]	Unclear	Yes	Unclear	Yes	No	No	No	No other major biases noted	Yes	No	**High** Serious concern around patient selection, no accounting for confounding, and conflicts of interest
Boon et al., 2002[58]	Unclear	Yes	Yes	Yes	No	No	No	No other major biases noted	No	Yes	**High** Serious concern around patient selection and comparability
Ellens et al., 2018[60]	No	Yes	Yes	Yes	No	No	No	Small sample sizes	No	No	**High** Serious concern around patient selection, comparability, and small sample sizes
Feldman et al., 2013[61]	Unclear	Yes	Unclear	Yes	Yes	No	No	No other major biases noted	Yes	Unclear	**High** Serious concern about lack of adjustment for confounding

Study	Participant Selection	Intervention Exposure	Appropriate Comparator	Outcomes	Outcome Assessor Masking	Confounding	Statistical Analysis	Other Biases	Interest Disclosure	Funding	Overall Risk of Bias Assessment Comments
George et al., 2005[62] Rush et al., 2005[74]	No	Yes	Yes	Yes	No	No	No	No other major biases noted	No	No	**High** Serious concern about patient populations drawn from different sources and industry funding
Gonen et al., 2015[63]	Yes	Yes	Yes	Yes	No	No	No	Small sample sizes	Yes	No	**High** Serious concern about small sample sizes and lack of adjusting for confounders
Harden et al., 2000[64]	Unclear	Yes	Yes	Yes	No	No	No	Small sample sizes	No	No	**High** Serious concern about lack of adjusting for confounders, small sample sizes and industry sponsorship
Helmers et al., 2003[65]	Yes	Yes	Yes	Yes	No	No	No	No other major biases noted	No	No	**High** Serious concern about lack of adjustment for confounding and industry funding
Hoppe et al., 2013[66]	Yes	Yes	Yes	Yes	No	No	Unclear	Small sample sizes	No	No	**High** Serious concern about a lack of adjusting for confounders, conflicts of interests, and small sample sizes

Study	Participant Selection	Intervention Exposure	Appropriate Comparator	Outcomes	Outcome Assessor Masking	Confounding	Statistical Analysis	Other Biases	Interest Disclosure	Funding	Overall Risk of Bias Assessment Comments
Jamy et al., 2019[67]	Unclear	Yes	Unclear	Yes	No	No	No	Small sample sizes	Unclear	No	**High** Serious concern about patient selection, comparability of groups, and small sample sizes
Kawai et al., 2017[68]	Not Applicable	Yes	Not Applicable	Yes	No	Not Applicable	No	No other major biases noted	Unclear	No	**Moderate** Some concern about the analysis
Kuba et al., 2013[69]	Unclear	Yes	Yes	Yes	No	No	No	Small sample sizes	Yes	No	**High** Serious concern about lack of adjusting for confounding, and industry funding. Also small sample sizes
McGlone et al., 2008[71]	Unclear	Yes	Unclear	Yes	No	No	No	Small sample sizes	Unclear	Yes	**High** Serious concern about patient selection, comparability, and small sample sizes
Morrison-Levy et al., 2018[72]	Unclear	Yes	Unclear	Yes	No	No	No	Small sample sizes	No	No	**High** Serious concern about patient selection, comparability and small sample sizes

Study	Participant Selection	Intervention Exposure	Appropriate Comparator	Outcomes	Outcome Assessor Masking	Confounding	Statistical Analysis	Other Biases	Interest Disclosure	Funding	Overall Risk of Bias Assessment Comments
Nei et al., 2006[73]	Unclear	Yes	Yes	Yes	No	No	No	No other major biases noted	No	No	**High** Serious concern about patient selection and comparability
Ryvlin et al., 2018[75]	Not Applicable	Yes	Not Applicable	Yes	Unclear	Unclear	Not Applicable	No other major biases noted	No	No	**High** Serious concern about analysis, industry funding and interests
Sherman et al., 2008[76]	Unclear	Yes	Unclear	Yes	No	No	No	Small sample sizes	No	Yes	**High** Serious concern about patient selection, comparability and small sample sizes
Van Lierde et al., 2015[77]	Yes	Yes	Yes	Yes	No	No	No	Small sample sizes	No	No	**High** Serious concern about small sample size, and lack of reporting around interests and funding
You et al., 2008[55]	Unclear	Yes	Yes	Yes	No	No	No	Small sample sizes	No	No	**High** Serious concern about the lack of reporting of interests, small sample sizes and lack of adjusting for confounders

Table D3. Risk of Bias: Economic Studies

Part 1

Citation	Target Population	Perspective	Time Horizon	Discount Rate	Comparators	Modeling	Effectiveness
Fallah et al., 2016[88]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes
Purser et al., 2018[89]	Yes	Yes	Yes	No	Yes	No	Yes

Part 2

Citation	Outcomes	Resource Use/Costs	Uncertainty	Results	Interest Disclosure	Funding Source	Overall Risk of Bias Assessment Comments
Fallah et al., 2016[88]	Yes	Yes	Yes	Unclear	Yes	Yes	**Moderate** Some concern around the lack of detail on the modelling approach Also concern about generalizability
Purser et al., 2018[89]	Yes	Yes	Unclear	No	No	No	**Moderate** Some concern about conflicts of interest and the simplistic modeling approach

Table D4. Methodological Quality: Guidelines

Guideline Developer, Year	Rigor of Development: Evidence	Rigor of Development: Recommendations	Editorial Independence	Scope & Purpose	Stakeholder Involvement	Clarity & Presentation	Applicability	Overall Assessment
Epilepsy								
Australian Government Medical Services Advisory Committee (MSAC), 2016[91]	Poor	Fair	Fair	Fair	Poor	Poor	Fair	**Poor**
Epilepsy Implementation Task Force, 2016[92]	Poor	Poor	Fair	Good	Fair	Poor	Poor	**Poor**
National Institute for Health and Care Excellence, 2012[93] (assessed as current in	Good	Good	Good	Good	Good	Good	Good	**Good**

Guideline Developer, Year	Rigor of Development: Evidence	Rigor of Development: Recommendations	Editorial Independence	Scope & Purpose	Stakeholder Involvement	Clarity & Presentation	Applicability	Overall Assessment
2014 with an update in progress)								
Scottish Intercollegiate Guidelines Network (SIGN), 2015[94]	Fair	Good	Fair	Good	Good	Good	Fair	**Good**
Task Force Report for the International League Against Epilepsy (ILAE) Commission of Pediatrics, 2015[95]	Fair	Fair	Fair	Fair	Poor	Fair	Fair	**Fair**
Wirrel et al., 2017 on behalf of a North American Consensus Panel[96]	Poor	Poor	Fair	Fair	Poor	Fair	Poor	**Poor**
Treatment-resistant Depression								
Canadian Network for Mood and Anxiety Treatments (CANMAT), 2016[97]	Fair	Poor	Fair	Fair	Poor	Poor	Poor	**Poor**
Department of Veterans Affairs, Department of Defense, 2016[98]	Fair	Good	Good	Good	Fair	Good	Fair	**Fair**
Australian Government Medical Services Advisory Committee (MSAC), 2018[99]	Poor	Fair	Fair	Fair	Poor	Poor	Fair	**Poor**
Royal Australian and New Zealand College of Psychiatrists, 2015[100]	Fair	Fair	Fair	Good	Good	Fair	Poor	**Fair**
Working Group of the Clinical Practice Guideline on the Management of Depression in Adults, 2014[101]	Good	Fair	Fair	Good	Good	Good	Fair	**Good**

Appendix E. GRADE Quality of Evidence

Epilepsy

Effectiveness

Table E1. GRADE Profile: Effectiveness of VNS for Epilepsy

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Certainty of Evidence Rating
High-stimulation VNS vs. Low-stimulation VNS								
Outcome: Reduction of 50% or More in Seizure Frequency								
N = 351 3 RCTs[80,82,87]	Serious (-1) See Risk of Bias assessment	Not serious	Not serious	Serious (-1) Based on a 25% MID	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs) Also note the sensitivity to missing data in the worst case analysis	RR, 1.62; 95% CI, 1.05 to 2.49	⨁⨁◯◯ LOW
Outcome: Mean Change in Seizure Frequency								
N = 9 1 RCT[51]	Very Serious (-2) See Risk of Bias assessment	Not serious (not assessable as only 1 study)	Not serious	Serious (-1) Wide CIs	Not assessed	Downgraded 2 levels for risk of bias, and 1 level for imprecision (i.e., wide CIs)	MD -36.08; 95% CI, -71.34 to -0.82	⨁◯◯◯ VERY LOW
Outcome: Seizure Freedom								
N = 312 2 RCTs[80,87]	Serious (-1) See Risk of Bias assessment	Not serious	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	1 participant receiving high-stimulation VNS and no participants in the low-stimulation groups became seizure free	⨁⨁◯◯ LOW

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Certainty of Evidence Rating
VNS vs. Treatment as Usual or Ongoing Medication								
Outcome: Reduction of 50% or More in Seizure Frequency								
N = 112 1 RCT[86]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study)	Not serious	Very Serious (-2) Based on a 25% threshold	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., wide CIs) Also note the sensitivity to missing data in the worst case analysis	RR 1.53; 95% CI, 0.63 to 3.74	⨁◯◯◯ VERY LOW
Outcome: Seizure Frequency (various measures)								
N = 216 4 NRSs[58,63,64,66]	Serious (-1) See Risk of Bias assessment	Not serious	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	VNS is associated with greater improvements in seizure frequency than treatment as usual or ongoing medication	⨁◯◯◯ VERY LOW
Outcome: Seizure Freedom								
N = 216 4 NRSs[58,63,64,66]	Serious (-1) See Risk of Bias assessment	Not serious	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	VNS does not appear to be associated with higher rates of seizure freedom than treatment as usual or ongoing medication	⨁◯◯◯ VERY LOW
VNS vs. Surgery								
Outcome: Seizure Frequency (various measures)								
N = 192 4 NRSs[55,69,72,73]	Serious (-1) See Risk of Bias assessment	Serious (-1) There is heterogeneity in the study findings	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and	VNS may be associated with similar improvements in seizure frequency than surgery, but surgery may be more	⨁◯◯◯ VERY LOW

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Certainty of Evidence Rating
						imprecision (i.e., not assessable)	effective for some patients or specific epilepsies	
Outcome: Seizure Freedom								
N = 252 5 NRSs[55,58,69,72,73]	Serious (-1) See Risk of Bias assessment	Serious (-1) There is heterogeneity in the study findings	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)	Surgery may be associated with higher rates of seizure freedom than VNS, but results are not consistent	⨁◯◯◯ VERY LOW
VNS vs. Responsive Neurostimulation								
Outcome: Seizure Frequency (various measures)								
N = 73 2 NRSs[60,67]	Serious (-1) See Risk of Bias assessment	Serious (-1) There is heterogeneity in the study findings	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)	VNS may be associated with similar improvements in seizure frequency than responsive neurostimulation, but surgery may be more effective for some patients	⨁◯◯◯ VERY LOW
Outcome: Seizure Freedom								
N = 73 2 NRSs[60,67]	Serious (-1) See Risk of Bias assessment	Serious (-1) There is heterogeneity in the study findings	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias, inconsistency (i.e., differences between studies) and imprecision (i.e., not assessable)	VNS may be associated with lower rates of seizure freedom than responsive neurostimulation, but results are not consistent	⨁◯◯◯ VERY LOW

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

Table E2. GRADE Profile: Effectiveness of tVNS for Epilepsy

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Certainty of Evidence Rating
High-stimulation tVNS vs. Low-stimulation tVNS								
Outcome: Reduction of 50% or More in Seizure Frequency								
N = 76 1 RCT[79]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study)	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 1.05; 95% CI, 0.50 to 2.24	⨁◯◯◯ VERY LOW
Outcome: Seizure Freedom								
N = 76 1 RCT[79]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study)	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	2.7% in the high-stimulation tVNS group and 7.7% in the low-stimulation group became seizure free	⨁⨁◯◯ LOW
Outcome: Seizure Severity								
N = 76 1 RCT[79]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study)	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	Mean change in severity score: 1.56, high-stimulation; 0.83, low-stimulation; *P* > .05 between groups	⨁⨁◯◯ LOW

Abbreviations. CI: confidence interval; MD: mean difference; MID: minimal important difference; NRS: nonrandomized study; RCT: randomized controlled trial; RR: risk ratio; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

Harms

Table E3. GRADE Profile: Harms of VNS for Epilepsy

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
High-stimulation VNS vs. Low-stimulation VNS								
Outcome: Treatment Withdrawals								
N = 353 3 RCTs[80,82,87]	Serious (-1) See Risk of Bias assessment	Not serious	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 2.56; 95% CI, 0.51 to 12.71	⨁◯◯◯ VERY LOW
Outcome: Voice Alteration or Hoarseness								
N = 312 2 RCTs[80,87]	Serious (-1) See Risk of Bias assessment	Not serious	Not serious	Not serious	Not assessed	Downgraded 1 level for risk of bias	RR 2.32; 95% CI, 1.56 to 3.45	⨁⨁⨁◯ MODERATE
Outcome: Cough								
N = 312 2 RCTs[80,87]	Serious (-1) See Risk of Bias assessment	Not serious	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 1.04; 95% CI, 0.70 to 1.56	⨁◯◯◯ VERY LOW
Outcome: Dyspnea								
N = 312 2 RCTs[80,87]	Serious (-1) See Risk of Bias assessment	Not serious	Not serious	Serious (-1) Based on a 25% MID	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)	RR 2.45; 95% CI, 1.07 to 5.60	⨁⨁◯◯ LOW
Outcome: Pain								
N = 312 2 RCTs[80,87]	Serious (-1) See Risk of Bias assessment	Not serious	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 1.01; 95% CI, 0.60 to 1.68	⨁◯◯◯ VERY LOW

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
Outcome: Paresthesias								
N = 312 2 RCTs[80,87]	Serious (-1) See Risk of Bias assessment	Not serious	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 0.78; 95% CI, 0.39 to 1.53	⨁◯◯◯ VERY LOW
Outcome: Nausea								
N = 312 2 RCTs[80,87]	Serious (-1) See Risk of Bias assessment	Not serious	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 0.72; 95% CI, 0.32 to 1.62	⨁◯◯◯ VERY LOW
Outcome: Headache								
N = 312 2 RCTs[80,87]	Serious (-1) See Risk of Bias assessment	Not serious	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 0.90; 95% CI, 0.48 to 1.69	⨁◯◯◯ VERY LOW
VNS vs. Treatment as Usual								
Outcome: Treatment Withdrawals								
N = 112 1 RCT[86]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study)	Not serious	Serious (-1) Based on a 25% MID	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)	RR 0.84; 95% CI, 0.59 to 1.20	⨁⨁◯◯ LOW
Outcome: Voice Alteration or Hoarseness								
N = 112 1 RCT[86]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 18.24; 95% CI, 0.44 to 750.38	⨁◯◯◯ VERY LOW

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
Outcome: Cough								
N = 112 1 RCT[86]	Not reported							Not Applicable
Outcome: Dyspnea								
N = 112 1 RCT[86]	Not reported							Not Applicable
Outcome: Pain								
N = 112 1 RCT[86]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 7.51; 95% CI, 0.16 to 357.94	⨁◯◯◯ VERY LOW
Outcome: Paresthesias								
N = 112 1 RCT[86]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 7.51; 95% CI, 0.16 to 357.94	⨁◯◯◯ VERY LOW
Outcome: Nausea								
N = 112 1 RCT[86]	Not reported							Not Applicable
Outcome: Headache								
N = 112 1 RCT[86]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 7.51; 95% CI, 0.16 to 357.94	⨁◯◯◯ VERY LOW

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

Table E4. GRADE Profile: Harms of tVNS for Epilepsy

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
High-stimulation tVNS vs. Low-stimulation tVNS								
Outcome: Treatment Withdrawals								
N = 76 1 RCT[79]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 1.32; 95% CI, 0.58 to 2.97	⨁◯◯◯ VERY LOW
Outcome: Voice Alteration or Hoarseness								
N = 76 1 RCT[79]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	None were observed	⨁⨁◯◯ LOW
Outcome: Cough								
N = 76 1 RCT[79]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	None were observed	⨁⨁◯◯ LOW
Outcome: Dyspnea								
N = 76 1 RCT[79]	Not reported							Not Applicable
Outcome: Pain								
N = 76 1 RCT[79]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 2.11; 95% CI, 0.38 to 11.81	⨁◯◯◯ VERY LOW
Outcome: Paresthesias								
N = 76 1 RCT[79]	Not reported							Not Applicable

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
Outcome: Nausea								
N = 76 1 RCT[79]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 1.05; 95% CI, 0.14 to 7.93	⨁◯◯◯ VERY LOW
Outcome: Headache								
N = 76 1 RCT[79]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 0.90; 95% CI, 0.40 to 2.06	⨁◯◯◯ VERY LOW

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

Cost-Effectiveness

Table E5. GRADE Profile: Cost-Effectiveness of VNS for Epilepsy

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
Outcome: Cost-Effectiveness								
N = 1 hypothetical cohort 1 cost-utility analysis[88]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study	Serious (-1) Limited to a specific condition	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias, indirectness (i.e., tuberous sclerosis complex only) and imprecision (i.e., not assessable)	VNS was more costly and less effective than other strategies for children who have not responded to 2 or 3 AEDs	⨁◯◯◯ VERY LOW
N = 1,536 1 budget impact study[89]	Serious (-1) See Risk of Bias assessment	Not serious (not assessable as only 1 study	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias, indirectness, and imprecision (i.e., not assessable)	VNS was associated with a reduction in costs over 5 years compared with AEDs alone	⨁◯◯◯ VERY LOW

Abbreviations. AED: antiepileptic drug; QALY: quality-adjusted life-year; VNS: vagal nerve stimulation; WTP: willingness-to-pay. Note. Cost-utility analyses started at HIGH and budget impact studies as LOW in the GRADE framework.

Depression

Effectiveness

Table E6. GRADE Profile: Effectiveness of VNS for Depression

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
High-stimulation VNS vs. Low-stimulation VNS								
Outcome: Depression Severity, Measured on the IDS-C								
N = 209 1 RCT[78]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	No difference between 3 VNS stimulation protocols	⊕⊕◯◯ LOW
Outcome: Suicide								
N = 224 1 RCT[78]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 0.98; 95% CI, 0.06 to 15.51	⊕◯◯◯ VERY LOW
Outcome: Attempted Suicide								
N = 224 1 RCT[78]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 0.56; 95% CI, 0.17 to 1.86	⊕◯◯◯ VERY LOW
Outcome: Response, Defined as 50% Reduction or More, Measured on the MADRS								
N = 224 1 RCT[78]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Serious (-1) Based on a 25% MID	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)	RR 1.84; 95% CI, 1.07 to 3.18	⊕⊕◯◯ LOW

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
VNS vs. Sham VNS								
Outcome: Depression Severity, Measured on the HRSD								
N = 222 1 RCT[85]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Not serious	Not assessed	Downgraded 1 level for risk of bias	Estimated difference -0.77; 95% CI, -2.34 to 0.80	⊕⊕⊕◯ MODERATE
Outcome: Depression Severity, Measured on the IDS-SR								
N = 222 1 RCT[85]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Not serious	Not assessed	Downgraded 1 level for risk of bias	Estimated difference -2.37; 95% CI, -4.78 to 0.03	⊕⊕⊕◯ MODERATE
Outcome: Suicide								
N = 235 1 RCT[85]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 2.92; 95% CI, 0.12 to 71.08	⊕◯◯◯ VERY LOW
Outcome: Response, Defined as 50% Reduction or More, Measured on the MADRS								
N = 222 1 RCT[85]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 1.39; 95% CI, 0.70 to 2.78	⊕◯◯◯ VERY LOW
VNS+TAU vs. TAU								
Outcome: Mean Difference in Reduction of Depressive Symptoms, Measured on the IDS-SR								
N = 329 1 NRS[62]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	VNS+TAU was associated with a greater reduction in depressive symptoms than TAU alone	⊕◯◯◯ VERY LOW

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
							However, the difference may not be clinically meaningful	
Outcome: Attempted Suicide or Self-inflicted Injury								
N = 12,853 1 NRS[61]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	VNS may be associated with higher rates of attempted suicide or self-inflicted injury	⨁◯◯◯ VERY LOW
Outcome: Mortality								
N = 13,648 2 NRS[56,61]	Serious (-1) See Risk of Bias assessment	Serious (-1) Differences in findings	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias, inconsistency, and imprecision (i.e., not assessable)	VNS may be associated with lower mortality rates, but study results are not consistent	⨁◯◯◯ VERY LOW

Abbreviations. CI: confidence interval; IDS-C: Inventory of Depressive Symptomatology-Clinician Administered; HRSD: Hamilton Rating Scale for Depression; IDS-SR: Inventory of Depressive Symptomatology Self Report; MADRS: Montgomery-Åsberg Depression Rating Scale; MID: minimal important difference; NRS: nonrandomized study; RCT: randomized controlled trial; RR: risk ratio; TAU: treatment as usual; VNS: vagal nerve stimulation. Note. Nonrandomized studies start at LOW in the GRADE framework.

Table E7. GRADE Profile: Effectiveness of tVNS for Depression

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
tVNS vs. Sham tVNS								
Outcome: Depression Severity, Measured on the HRSD								
N = 37 1 RCT[81]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	No difference between tVNS and sham VNS	⊕⊕◯◯ LOW
Outcome: Depression Severity, Measured on the BDI								
N = 37 1 RCT[81]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	tVNS was associated with a clinically meaningful change in depression	⊕⊕◯◯ LOW

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

Harms

Table E8. GRADE Profile: Harms of VNS for Depression

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
High-stimulation VNS vs. Low-stimulation VNS								
Outcome: Withdrawals								
N = 224 1 RCT[78]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 0.39; 95% CI, 0.08 to 1.98	⨁◯◯◯ VERY LOW
Outcome: Voice Alteration or Hoarseness								
N = 224 1 RCT[78]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Serious (-1) Based on a 25% MID	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)	RR 1.19;95% CI, 0.95 to 1.49	⨁⨁◯◯ LOW
Outcome: Cough								
N = 224 1 RCT[78]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 1.02; 95% CI, 0.56 to 1.86	⨁◯◯◯ VERY LOW
Outcome: Dyspnea								
N = 224 1 RCT[78]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 1.13; 95% CI, 0.68 to 1.88	⨁◯◯◯ VERY LOW

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
Outcome: Pain								
N = 224 1 RCT[78]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Serious (-1) Based on a 25% MID	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)	RR 1.65; 95% CI, 0.99 to 2.74	⊕⊕◯◯ LOW
Outcome: Paresthesias								
N = 224 1 RCT[78]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 1.24; 95% CI, 0.74 to 2.07	⊕◯◯◯ VERY LOW
Outcome: Nausea								
N = 224 1 RCT[78]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 0.59; 95% CI, 0.21 to 1.65	⊕◯◯◯ VERY LOW
Outcome: Headache								
N = 224 1 RCT[78]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 1.09; 95% CI, 0.52 to 2.27	⊕◯◯◯ VERY LOW
VNS vs. Sham VNS								
Outcome: Withdrawals								
N = 222 1 RCT[85]	Serious (-1)	Not serious	Not serious	Very serious (-2)	Not assessed	Downgraded 1 level for risk of bias and 2 levels	RR 6.88; 95% CI, 0.36 to 131.58	⊕◯◯◯ VERY LOW

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
	See Risk of Bias assessment	Not assessable as only 1 study		Based on a 25% MID		for imprecision (i.e., very wide CIs)		
Outcome: Voice Alteration or Hoarseness								
N = 235 1 RCT[85]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Not serious	Not assessed	Downgraded 1 level for risk of bias	RR 1.79; 95% CI, 1.27 to 2.54	⊕⊕⊕◯ MODERATE
Outcome: Cough								
N = 235 1 RCT[85]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Not serious	Not assessed	Downgraded 1 level for risk of bias	RR 3.10; 95% CI, 1.36 to 7.07	⊕⊕⊕◯ MODERATE
Outcome: Dyspnea								
N = 235 1 RCT[85]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Serious (-1) Based on a 25% MID	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)	RR 1.64; 95% CI, 0.78 to 3.45	⊕⊕◯◯ LOW
Outcome: Pain								
N = 235 1 RCT[85]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Serious (-1) Based on a 25% MID	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., wide CIs)	RR 2.03; 95% CI, 0.88 to 4.70	⊕⊕◯◯ LOW
Outcome: Paresthesias								
N = 235 1 RCT[85]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 1.54; 95% CI, 0.63 to 3.75	⊕◯◯◯ VERY LOW

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
Outcome: Nausea								
N = 235 1 RCT[85]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Very serious (-2) Based on a 25% MID	Not assessed	Downgraded 1 level for risk of bias and 2 levels for imprecision (i.e., very wide CIs)	RR 2.11; ,95% CI, 0.62 to 7.20	⨁◯◯◯ VERY LOW
Outcome: Headache								
N = 222 1 RCT[85]	Not reported							Not Applicable
VNS vs. TAU								
Outcome: Withdrawals								
N = 795 1 NRS[56]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Not serious	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias and imprecision (i.e., not assessable)	Completion rates were higher in the VNS+TAU group than in the TAU group, but formal statistical testing was not conducted	⨁◯◯◯ VERY LOW

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

Table E9. GRADE Profile: Harms of tVNS for Depression

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
tVNS vs. Sham tVNS								
Outcome: Overall Adverse Events								
N = 37 1 RCT[81]	Serious (-1) See Risk of Bias assessment	Not serious Not assessable as only 1 study	Serious (-1) Only high level events reported	Serious (-1) Not assessable	Not assessed	Downgraded 1 level each for risk of bias, indirectness (i.e., not reported by specific adverse event), and imprecision (i.e., not assessable)	No adverse events were observed or reported	⨁◯◯◯ VERY LOW

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

Cost-Effectiveness

Table E10. GRADE Profile: Cost-Effectiveness of VNS for Depression

Number of Participants and Studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Comments	Effect	Overall Quality of Evidence Rating
Outcome: Cost-Effectiveness								
No studies were identified								Not Applicable

Appendix F. Best and Worst Case Sensitivity Analyses

Epilepsy

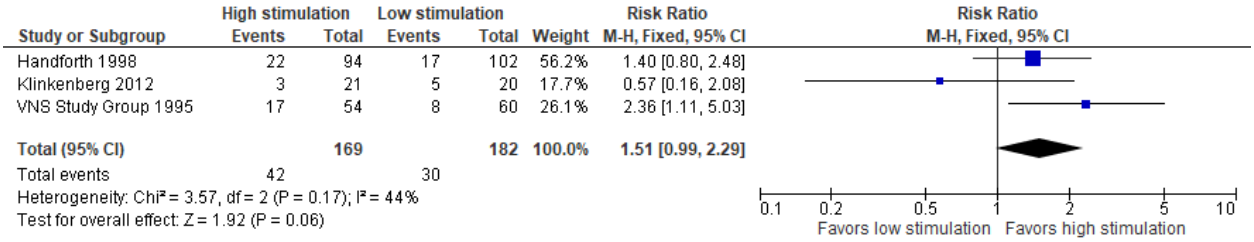

Figure F1. VNS High- vs. Low-stimulation, Outcome: 50% Responders Worst Case

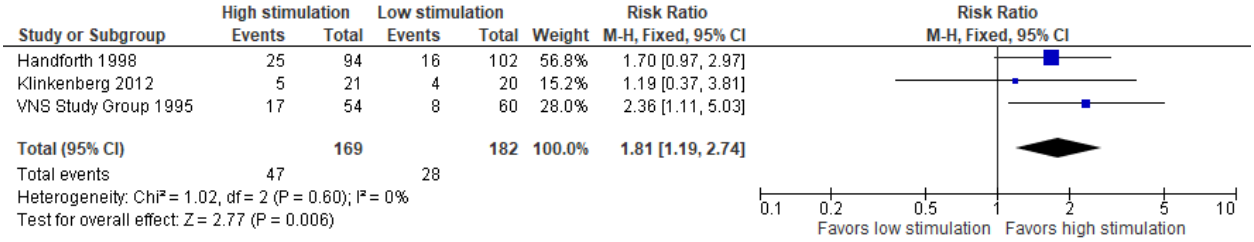

Figure F2. VNS High- vs. Low-stimulation, Outcome: 50% Responders Best Case

Figure F3. VNS vs. Treatment as Usual, Outcome: 50% Responders Worst Case

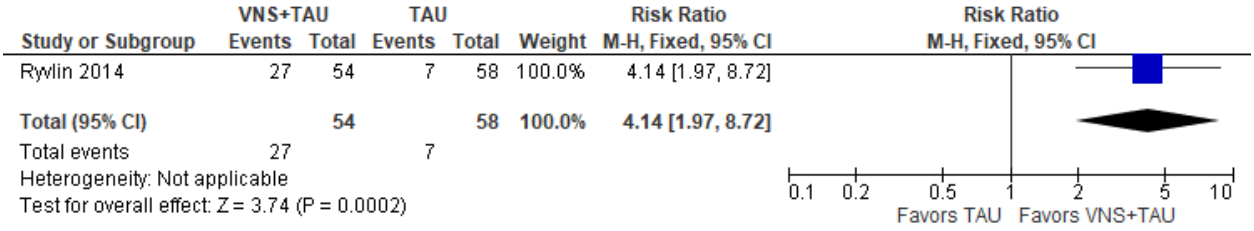

Figure F4. VNS vs. Treatment as Usual, Outcome: 50% Responders Best Case

Depression

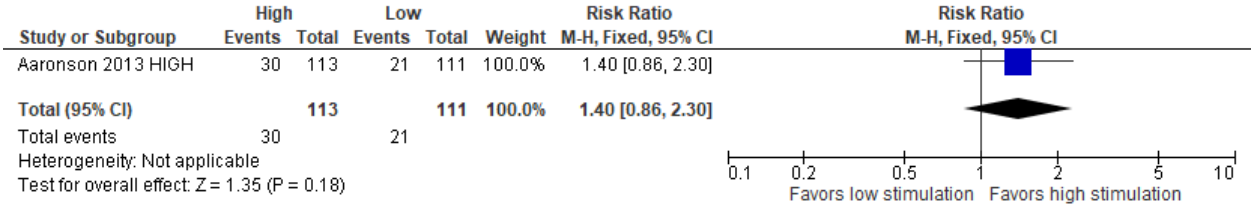

Figure F5. VNS High- vs. Low-stimulation, Outcome: 50% MADRS or More Worst Case

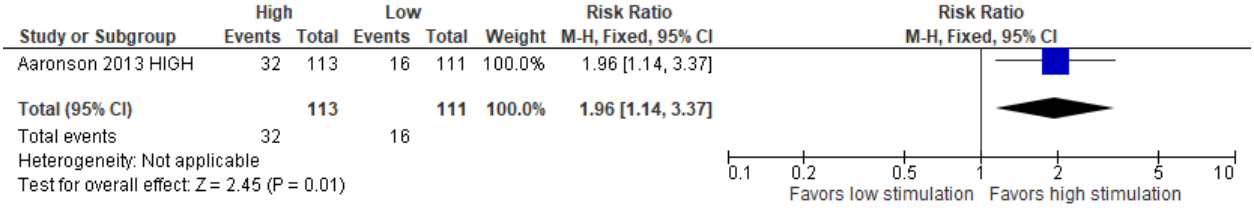

Figure F6. VNS High- vs. Low-stimulation, Outcome: 50% MADRS or More Best Case

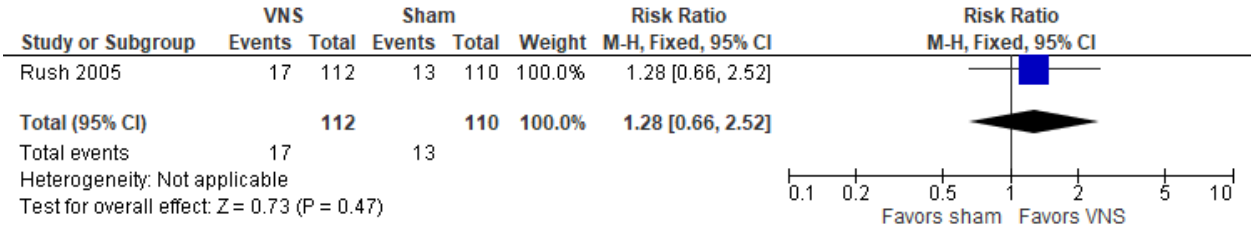

Figure F7. VNS vs. Sham, Outcome: 50% MADRS or More Worst Case

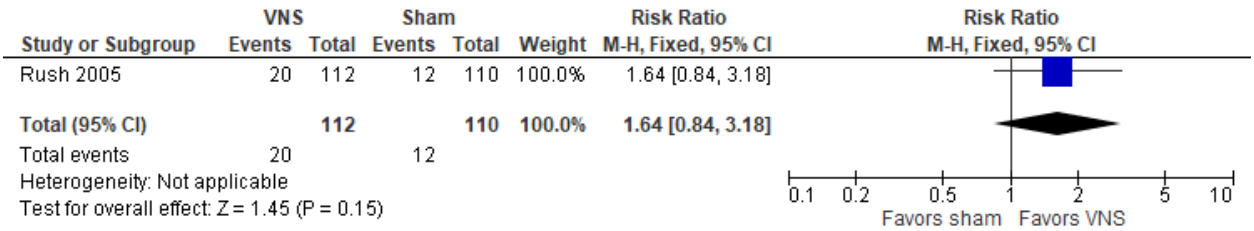

Figure F8. VNS vs. Sham, Outcome: 50% MADRS or More Best Case

Appendix G. MAUDE and Medical Device Recall Reports

Table G1. Reports on VNS and tVNS from the Medical Device Recall Database

See attachment for results from the U.S. FDA Manufacturer and User Facility Device Experience (MAUDE) database (pages G1-G381).

Table G2. Reports on VNS and tVNS from the Medical Device Recall Database

Device Name	Manufacturer	Recall Class	Classification Date	Reason for Recall
VNS Therapy SenTiva Generator System	LivaNova USA Inc	1	2019/12/20	LivaNova is recalling the VNS Therapy SenTiva Generator System due to an unintended reset error that causes the system to stop delivering VNS therapy. If device replacement is needed, there is a risk associated with additional surgery to replace the generator. LivaNova has received 14 reports of unexpected reset errors. 4 patients have required early revision surgery for failed devices. No deaths related to this issue have been reported. On July 31, 2019, LivaNova implemented additional mitigations and at this time, no reset errors have been observed since implementation of these mitigations. These additional mitigations are currently under review by the FDA.
Vagus Nerve Stimulation Therapy System	LivaNova USA Inc	2	2019/12/10	This recall is being initiated due to reports that that the therapy programming tablet with software version 1.5 errantly performs a normal mode diagnostic test instead of the selected system diagnostic test on Model 102 and Model 102R devices, if the output current is greater than 0.5 mA. This can result in false high impedance values during patient follow-up.
VNS Therapy, Sentiva,	LivaNova USA Inc	2	2019/11/07	Lead impedance values reported by the affected VNS generator will be higher compared to those reported by previous models. This is due to a change in the timing of when affected VNS generator takes the lead impedance measurement during diagnostic testing. As a result, normal impedance ranges for the affected VNS generator have shifted relative to the existing thresholds of 600-5300 ohms defined in labeling and as present in the programming software.
VNS Therapy Programming System	LivaNova USA Inc	2	2018/07/28	Unintended warning message displayed on generators programmed with a Model 3000 v.1.0.2.2 programmer.

Device Name	Manufacturer	Recall Class	Classification Date	Reason for Recall
VNS Therapy Programmer, Model 3000 v1.0 System	Cyberonics, Inc	2	2018/06/19	Certain Model 3000 programming events can result in miscalculation of parameters stored in the Models 103, 104, 105, and 106 generators. During these programming events, the miscalculations can lead to: • "Delivery of more stimulation than intended, resulting in painful stimulation or other common side effects (Model 106 only) • "No stimulation in the case of device disablement (Burst Watchdog Timeout), resulting in no therapy to the patient (Model 106 only) • "Delivery of less stimulation than intended, resulting in therapeutic settings not being achieved within device specification (Models 103, 104, 105, or 106); and/or • "Delays or absence of the 75% and 50% battery life indicators displayed by the programming software (Models 103, 104, 105, or 106).
VNS(R) Therapy Programmer	Cyberonics, Inc	2	2018/02/08	Two Model 3000 Programmers were distributed in error by prior to FDA approval of version 1.0.2.2 software.
Model 106 AspireSR Generators	Cyberonics, Inc	2	2017/08/11	Manufacturing process used to assemble the circuit board may result in some devices experiencing a faster than expected reduction in device longevity.
Model 105 Aspire HC¿ and Generators	Cyberonics, Inc	2	2017/08/11	Manufacturing process used to assemble the circuit board may result in some devices experiencing a faster than expected reduction in device longevity.
Cyberonics VNS Therapy AspireSR Generator, Model 106	Cyberonics, Inc	2	2016/01/19	Certain Model 106 Pulse Generators demonstrate delays in sensing during use of the 'Verify Heartbeat Detection' feature and exhibit the potential for decreased battery longevity.
VNS Therapy AspireSR Generator	Cyberonics, Inc	2	2016/01/15	Recall being initiated in response to three reports of "Burst Watchdog Timeout" events occurring with the Model 106 AspireSR Generator, resulting in a device reset condition where stimulation output is disabled.
Cyberonics VNS Therapy AspireSR Generator Model 106	Cyberonics, Inc	2	2015/11/17	Certain Model 106 Pulse Generators demonstrate delays in sensing during use of the 'Verify Heartbeat Detection' feature and exhibit potential for decreased battery longevity.
VNS Therapy Generator	Cyberonics, Inc	2	2015/04/27	The pulse generators have a lower battery longevity than specified in their design requirement as a result of the devices being inadvertently left in a programmed ON state during manufacture.
VNS Therapy AspireHC Pulse Generator	Cyberonics, Inc	2	2014/12/23	The recalled product was distributed with an incorrect serial number printed on the device's label.

Device Name	Manufacturer	Recall Class	Classification Date	Reason for Recall
VNS Therapy Aspire HC Generator and VNS	Cyberonics, Inc	2	2011/11/18	The devices are being recalled because the output current delivered to the vagus nerve is less than the design intent and there is a potential charge imbalance at the lead cathode and generator-can during stimulation.
Cyberonics	Cyberonics, Inc	2	2011/10/04	An investigation was initiated based on a report from the field in which an Intensive Follow-up Indicator message was unexpectedly received by a medical professional when using Model 250 version 8.0 software to interrogate a patient's Model 103 Generator.
Cyberonics	Cyberonics, Inc	2	2011/10/04	An investigation was initiated based on a report from the field in which an Intensive Follow-up Indicator message was unexpectedly received by a medical professional when using Model 250 version 8.0 software to interrogate a patient's Model 103 Generator.
VNS Therapy System	Cyberonics, Inc	2	2010/05/10	Battery life projection is inaccurate.
VNS Therapy Demipulse Generator and VNS Therapy Demipulse Duo Generator	Cyberonics, Inc	2	2010/01/14	Under certain conditions, product's battery life can be reduced.
Cyberonics VNS Therapy Programming M250 System	Cyberonics, Inc	2	2009/11/16	Some VNS Therapy System replacement Demipulse generators reporting low lead impedance readings. In rare instances, a system diagnostic test using Model 250 Programming Software (versions 7.1 and earlier) may report "Lead Impedance: OK" when a short-circuit condition exists.
VNS Therapy System Generator	Cyberonics, Inc	3	2009/04/22	Reset/disabling of the VNS Therapy Demipulse Generator and Demipulse Duo Generator due to magnet interference, resulting in the loss of stimulation.
VNS Therapy System Generator	Cyberonics, Inc	3	2009/04/22	Reset/disabling of the VNS Therapy Demipulse Generator and Demipulse Duo Generator due to magnet interference resulting in the loss of stimulation.
Cyberonics VNS Therapy System	Cyberonics, Inc	3	2008/01/28	Screen Freezes-- The Dell X5 Handheld PC screen will freeze caused due to incompatibility between the Microsoft 2002 OS and the model Dell X5 handheld computer. Once frozen, the handheld device becomes nonresponsive to user input.
VNS System Leads	Cyberonics, Inc	2	2007/11/27	Dissolution/Fractures to the leads of the VNS Therapy System
VNS System Leads	Cyberonics, Inc	2	2007/11/27	Dissolution/Fractures to the leads of the VNS Therapy System

Device Name	Manufacturer	Recall Class	Classification Date	Reason for Recall
Cyberonics VNS Therapy System	Cyberonics, Inc	2	2007/01/24 14:02:52	During programming, pulse generator may be inadvertently set to 8.0 mA output, regardless of the mA range selected by the clinician
Cyberonics VNS Therapy System	Cyberonics, Inc	2	2007/01/24 14:02:52	During programming, pulse generator may be inadvertently set to 8.0 mA output, regardless of the mA range selected by the clinician

Notes. Class 1: A situation where there is a reasonable chance that a product will cause serious health problems or death; Class 2: A situation where a product may cause a temporary or reversible health problem or where there is a slight chance that it will cause serious health problems or death; Class 3: A situation where a product is not likely to cause any health problem or injury. Abbreviations. FDA: U.S. Food and Drug Administration; tVNS: transcutaneous VNS; VNS: vagal nerve stimulation.

Appendix H. CMS Medicare Decision Memo

CMS is finalizing changes to the vagus nerve stimulation (VNS) NCD (160.18) for VNS for treatment resistant depression (TRD) that will expand Medicare coverage. The scope of this reconsideration is limited to VNS for TRD.

A. The Centers for Medicare & Medicaid Services (CMS) will cover FDA approved vagus nerve stimulation (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.

B. Covered Indications

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 ≥ 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 remission/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 ≥ 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).

a. 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.
b. The rationale for the study is well supported by available scientific and medical evidence.
c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
d. 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.
e. The study is sponsored by an organization or individual capable of completing it successfully.
f. 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.

g. All aspects of the study are conducted according to appropriate standards of scientific integrity.
h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
i. 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.
j. 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 accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), 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 effect 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.

Appendix I. Studies Registered at ClinicalTrials.gov

Epilepsy

Table I1. Ongoing Studies

Registered Clinical Trial Number	Title of Study	Study Completion Date	Status of Publications and Whether Study Eligible for Possible Inclusion in Systematic Review
NCT03529045[103]	Registry of subjects with drug resistant epilepsy and treated with the VNS therapy system (CORE-VNS)	March 2027	No published study; per the review protocol, the study would be eligible for this review.

Abbreviation. VNS: vagal nerve stimulation.

Depression

Table I2. Ongoing Studies

Registered Clinical Trial Number	Title of Study	Study Completion Date	Status of Publications and Whether Study Eligible for Possible Inclusion in Systematic Review
NCT03320304[104]	A study to assess effectiveness and efficiency of VNS therapy in patients with difficult to treat depression (RESTORE-LIFE)	December 2025	No published study; per the review protocol, the study would be eligible for this review
NCT03887715[105]	A prospective, multi-center, randomized controlled blinded trial demonstrating the safety and effectiveness of VNS therapy system as adjunctive therapy versus a no stimulation control in subjects with treatment-resistant depression (RECOVER)	December 2030	No published study; per the review protocol, the study would be eligible for this review

Abbreviation. VNS: vagal nerve stimulation.

Appendix J. Excluded Studies

See attachment for a list of excluded studies, with reasons for exclusion (pages J1-J22).

Appendix K. Washington State Utilization and Cost Data - Attachment

Population

Data represent paid or accepted claims for procedures and services associated with vagal nerve stimulation (VNS) procedures and services between July 1, 2016 and June 30, 2019. Administrative claims and encounter data from the following Washington State health programs were assessed: the Public Employees Benefit Board Uniform Medical Plan (PEBB/UMP), Medicaid managed care (MCO) and fee-for-service (FFS) plans, and the Department of Labor and Industries Workers' Compensation Plan.

To protect patient privacy, we do not include here the VNS-related procedures and services paid through the Department of Labor and Industries Workers' Compensation Plan, as the number of individuals who received these benefits did not meet the threshold for public reporting.

This assessment includes final paid and adjudicated claims, encounters, and bills; denied claims and bills or rejected encounters are excluded. Individuals who were dually eligible for both Medicare and Medicaid are excluded from the Medicaid program analysis. The PEBB/UMP experience focuses on claims for non-Medicare services.

Timeframe

Data are reported annually, according to the state fiscal year (SFY). A 6-month claims runout was observed to ensure data completeness and reliability.

Procedures Related to VNS Device Utilization

The assessment focuses on procedures and services related to VNS devices (e.g., implantation, removal, revision, monitoring) with a date of service between July 1, 2016 and June 30, 2019.

Individuals who had a qualifying procedure or service during the period, according to Current Procedural Terminology (CPT) code or Level II Healthcare Common Procedure Coding System (HCPCS) code, were extracted for analysis (Table K1).

Table K1. CPT and HCPCS Codes for VNS-related Procedures and Services

Code	Description
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array
61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays
61888	Revision or removal of cranial neurostimulator pulse generator or receiver
64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve
64568	Incision for implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
64569	Revision or replacement of cranial nerve (e.g., vagus nerve) neurostimulator electrode array, including connection to existing pulse generator
64570	Removal of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator
95976	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
95977	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group[s], interleaving, amplitude, pulse width, frequency [Hz], on/off cycling, burst, magnet mode, dose lockout, patient selectable parameters, responsive neurostimulation, detection algorithms, closed loop parameters, and passive parameters) by physician or other qualified health care professional; with complex cranial nerve neurostimulator pulse generator/transmitter programming by physician or other qualified health care professional
64565	Percutaneous implantation of neurostimulator electrode array; neuromuscular. Expired 01/01/2018.
95974	Electronic analysis of implanted neurostimulator pulse generator system. Expired 01/01/2019.
95975	Electronic analysis of implanted neurostimulator pulse generator system. Expired 01/01/2019.
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator
L8682	Implantable neurostimulator radiofrequency receiver
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension
L8689	External recharging system for battery (internal) for use with implantable neurostimulator

Abbreviations. CPT: Current Procedural Terminology; HCPCS: Healthcare Common Procedure Coding System; Hz: Hertz; VNS: vagal nerve stimulation.

Payments for Procedures Related to VNS

Includes procedures related to implantation, revision, removal, analysis and medical devices in the inpatient and outpatients settings. Payments do not include physician services for assessment and maintenance that are not identifiably specific to the device. Paid amounts are summed for the procedure or service by year and for the 3-year measurement period (Table K2.)

Table K2. Utilization of VNS-related Procedures and Services, by State Health Program (State Fiscal Years 2017-2019)

State Health Program	State Fiscal Year			Overall (3 Years)
Medicaid	2017	2018	2019	Unique individuals
Fee-for-Service (FFS)				
Annual members	139,173	111,414	111,222	120,603
Individuals with at least one VNS-related procedure	32	23	28	50
Female, N (%)	NR	NR	NR	17 (34)
Number of encounters with VNS-related procedure	62	57	84	203
Average encounters with VNS-related procedure	1.9	2.5	3.0	4.1
Max encounters with VNS-related procedure	8	13	18	20
Amount paid, VNS-related procedures	$31,804	$122,605	$70,566	$224,975
Average payments per individual	$994	$5,331	$2,520	$4,499
Managed Care (MCO)				
Annual members	1,579,124	1,570,142	1,532,692	1,560,653
Individuals with at least one VNS-related procedure/service	224	206	255	472
Female, N (%)	111 (50)	114 (55)	128 (50)	239 (51)
Number of encounters with VNS-related procedure	550	450	518	1518
Average encounters with VNS-related procedure	2.5	2.2	2.0	3.2
Max encounters with VNS-related procedure	15	9	9	17
Amount paid (estimated), VNS-related procedures	$885,968	$830,380	$1,079,384	$2,795,733
Average payments per individual	$3,955	$4,031	$4,233	$5,923
Public Employees Benefit Board Uniform Medical Plan (PEBB/UMP)				
Annual members (non-retirees/COBRA)	187,673	196,020	198,347	194,013
Individuals with at least one VNS-related procedure/service		25	33	49
Female, N (%)		NR	NR	NR
Number of encounters with VNS-related procedure		55	64	119
Average encounters with VNS-related procedure		2.2	1.9	2.4
Max encounters with VNS-related procedure		10	8	15
Amount paid, VNS-related procedures		$477,218	$567,014	$1,044,232
Average payments per individual		$19,089	$17,182	$21,311
Washington State Department of Labor and Industries (L&I)				
Workers' compensation claims by year	126,524	124,081	124,959	125,188
Individuals with at least one VNS-related procedure/service	NR			

Notes. Annual members for Medicaid excludes members who are dually eligible for Medicaid and Medicare. Three year reference population values reflect average annual members. Small numbers suppressed to protect patient privacy. Encounter defined as a date of service associated with at least one VNS procedure or service. Amount paid reflects all claims submitted with the procedure code for the date of service, and includes professional, facility and ancillary claims (such as durable medical equipment). Managed care amount paid reflects an estimate of the amount paid for the procedure. Individuals who had a procedure in more than one year are only counted once in the "Overall" summary. Abbreviations. COBRA: Consolidated Omnibus Budget Reconciliation Act; NR: not reported; VNS: vagal nerve stimulation.

Table K3. Beneficiaries With at Least 1 VNS-related Procedure, State Fiscal Years 2017-2019

Medicaid (FFS and MCO) Beneficiaries			
Age	Female, N (%)	Male, N (%)	Total, N
20 years old and under	96 (44)	121 (56)	**217**
21-44 years old	105 (46)	122 (54)	**227**
45 years old and over	54 (69)	24 (31)	**78**
Total	**255 (49)**	**267 (51)**	**522**

Abbreviations. FFS: fee-for-service; MCO: managed care organization; VNS: vagal nerve stimulation.

Paid Amounts for Specific VNS Procedures

Overall, the average amount paid for the VNS implant procedure among PEBB/UMP members (inclusive of professional and related facility fees) was $31,317. However, the number of claims for VNS implant procedures for the two years of PEBB/UMP data did not meet the threshold for more detailed public reporting.

Table K4. Utilization of VNS Implant Procedures

Medicaid (FFS and MCO)						
CPT codes 61885, 64553						
Year (SFY)	Age	Unique patients	Procedures Performed	Allowed amount	Paid amount	Average paid amount, per procedure
2017-2019	All	134	135	$1,581,267	$1,386,857	$10,273
	4-11 years	28	29	$304,103	$303,609	$10,469
2017	All	43	44	$443,632	$380,728	$8,653
2018	All	42	42	$564,285	$470,202	$11,195
2019	All	49	49	$573,349	$535,928	$10,937

Abbreviations. CPT: Current Procedural Terminology; FFS: fee-for-service; MCO: managed care organization; SFY: state fiscal year; VNS: vagal nerve stimulation.

Table K5. Utilization of VNS-related Procedures for Patients Who Received a VNS Implant in SFY 2017

Medicaid (FFS and MCO)				
All VNS-related CPT codes				
Year (SFY)	Patients	Encounters	Paid amount	Average paid amount, per patient
2017	43	230	$418,384	$9,730
2018	26	72	$10,910	$420
2019	18	38	$3,288	$183

Abbreviations. CPT: Current Procedural Terminology; FFS: fee-for-service; MCO: managed care organization; SFY: state fiscal year; VNS: vagal nerve stimulation.

Table K6. Utilization of VNS Maintenance and Monitoring Procedures

Medicaid (FFS and MCO)						
Year (SFY)	Age	Unique patients	Procedures	Allowed amount	Paid amount	Average paid amount
Generator and Battery Replacement (CPT 61885, 61886)						
2017-2019	All	182	196	$1,718,109	$1,416,047	$7,225
2017	All	60	61	$516,930	$452,566	$7,419
2018	All	60	61	$533,397	$417,063	$6,837
2019	All	70	74	$667,782	$546,418	$7,384
Generator and Electrode Removal Only (CPT 64570), or Generator Revision or Removal (CPT 61888)						
2017-2019	All	26	35	$48,981	$41,546	$1,187
Electronic Analysis of Device (CPT 95976, 95977, 95974, 95975)						
2017-2019	All	413	1442	$195,230	$171,978	$119
2017	All	213	524	$68,419	$63,267	$121
2018	All	186	420	$66,508	$57,832	$138
2019	All	236	498	$60,303	$50,879	$102

Notes. Tables provide approximate paid amounts for select VNS procedures that had sufficient counts to support public reporting. Amount paid reflects all claims submitted with the procedure code for the date of service, and includes professional, facility and ancillary claims (such as durable medical equipment). Abbreviations. CPT: Current Procedural Terminology; FFS: fee-for-service; MCO: managed care organization; SFY: state fiscal year; VNS: vagal nerve stimulation.

Table K7. Maximum Allowable Cost by HCPCS/CPT Code, By State Health Program and Setting

Code	Description	Medicaid FFS		L&I	
		Non-Facility	Facility	Non-Facility	Facility
61885	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to a single electrode array	$310	$310	$979	$979
61886	Insertion or replacement of cranial neurostimulator pulse generator or receiver, direct or inductive coupling; with connection to 2 or more electrode arrays	$513	$513	$1,608	$1,608
61888	Revision or removal of cranial neurostimulator pulse generator or receiver	$238	$238	$754	$754
64553	Percutaneous implantation of neurostimulator electrode array; cranial nerve	$1,042	$211	$2,146	$703
64568	Incision for implantation of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator	$381	$381	$1,209	$1,209
64569	Revision or replacement of cranial nerve (e.g., vagus nerve) neurostimulator electrode array, including connection to existing pulse generator	$456	$456	$1,456	$1,456
64570	Removal of cranial nerve (e.g., vagus nerve) neurostimulator electrode array and pulse generator	$439	$439	$1,401	$1,401
95976	Electronic analysis of implanted neurostimulator pulse generator/transmitter by physician or other qualified health care professional; with simple cranial nerve neurostimulator pulse generator/transmitter programming	$24	$24	Not Covered	Not Covered
95977	Electronic analysis of implanted neurostimulator pulse generator/transmitter by physician or other qualified health care professional; with complex cranial nerve neurostimulator pulse generator/transmitter programming	$32	$32	Not Covered	Not Covered
64565	Percutaneous implantation of neurostimulator electrode array; neuromuscular.	Expired 1/2018.			
95974	Electronic analysis of implanted neurostimulator pulse generator system.	Expired 1/2019. Replaced by 95976.			
95975	Electronic analysis of implanted neurostimulator pulse generator system.	Expired 1/2019. Replaced by 95977.			
L8680	Implantable neurostimulator electrode, each	Covered (PA); EAPG.		$563	$563
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator	Covered (PA); EAPG.		$1,304	$1,304

Code	Description	Medicaid FFS		L&I	
		Non-Facility	Facility	Non-Facility	Facility
L8682	Implantable neurostimulator radiofrequency receiver	Covered (PA); EAPG.		$7,348	$7,348
L8683	Radiofrequency transmitter (external) for use with implantable neurostimulator radiofrequency receiver	Covered (PA); EAPG.		$6,468	$6,468
L8685	Implantable neurostimulator pulse generator, single array, rechargeable, includes extension	Covered (PA); EAPG.		$16,024	$16,024
L8686	Implantable neurostimulator pulse generator, single array, non-rechargeable, includes extension	Covered (PA); EAPG.		$10,225	$10,225
L8687	Implantable neurostimulator pulse generator, dual array, rechargeable, includes extension	Covered (PA); EAPG.		$20,854	$20,854
L8688	Implantable neurostimulator pulse generator, dual array, non-rechargeable, includes extension	Covered (PA); EAPG.		$13,306	$13,306
L8689	External recharging system for battery (internal) for use with implantable neurostimulator	Covered (PA); EAPG.		$2,047	$2,047

Sources. Medicaid FFS Fee Schedule (webpage accessed April 20, 2020); L&I provider fee schedule (accessed April 20, 2020). Note. PEBB/UMP fees are confidential and not publicly available (proprietary). Abbreviations. CPT: Current Procedural Terminology; EAPG: enhanced ambulatory patient groups; HCPCS: Healthcare Common Procedure Coding System; L&I: WA Department of Labor and Industries Workers' Compensation Plan; PA: prior authorization.