Molina Clinical Policy
Neurostimulation Treatments for Epilepsy: Policy No. 466

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OVERVIEW

Epilepsy, one of the most common neurological conditions worldwide, is characterized by recurrent seizures. Seizures are defined as paroxysmal disorders of the central nervous system characterized by abnormal cerebral neuronal discharge, with or without loss of consciousness. Most seizures can be categorized as either focal or generalized according to whether the onset of electrical activity involves both sides or a focal region of the brain. Epilepsy has a myriad of causes, such as brain tumors, metabolic disorders, hypoxic brain injuries, strokes, infections, and certain genetic syndromes; however, most cases are idiopathic in origin. Anti-epileptic medications are the first line of defense in treating seizure disorders, however, many cases remain uncontrolled even in the setting of a rigorous drug regimen. Since epilepsy carries an increased risk for premature death, controlling the condition is paramount to patient's overall health and wellbeing.

Refractory epilepsy, also referred to as intractable or drug-resistant epilepsy, is used to characterize patients with epilepsy whose seizures do not effectively respond to anti-epileptic medications. Refractory epilepsy may affect up to 20 to 40% of epileptic patients, or about 400,000 persons in the United States, the majority of which present with partial/focal-onset seizures, especially those associated with temporal lobe epilepsy (Gummadavelli et al. 2022; Sirven 2024). Recent International League Against Epilepsy (Jehi et al. 2022) expert consensus recommendation early referral for epilepsy resective surgery for patients with refractory epilepsy as soon as drug resistance is established. When surgery is contraindicated or ineffective, however, neuromodulation has emerged as a treatment option.

Vagus Nerve Stimulation (VNS) is a neuromodulatory antiepileptic therapy that involves the implantation of a subcutaneous programmable device connected to leads placed around the vagus nerve. The vagus nerve is then continuously stimulated in a programmable pattern. Most reported complications associated with VNS are hoarseness, neck and throat pain, nausea, vomiting, dyspnea, and coughing (Schachter and Sirven 2024).

Deep Brain Stimulation (DBS) is a neurointerventional procedure involving the implantation of electrodes and a device that transmits electrical pulses to areas of the brain. The electrodes are attached to a pulse generator and delivers a predetermined (open loop) program of electrical stimulation to subcortical deep brain structures. Areas of the brain that may be targeted are the anterior and centromedian thalamic nuclei, the subthalamic nucleus, the caudate, hippocampus, and the cerebellum (Sirven 2024).

Responsive Neurostimulation (RNS), also referred to as responsive cortical stimulation, is an epileptic treatment which involves the surgical implantation of a cortical neurostimulator that senses and records brain activity through electrode-containing leads that are placed at the seizure focus. The closed–loop device can detect specific patterns of epileptogenic activity and delivering focal stimulation to abort seizure activity. The system is intended to reduce the frequency of seizures in individuals with medically refractory epilepsy that persists in severity and/or frequency despite a reasonable trial of two or more antiepileptic medications (Sirven 2024).

Regulatory Status

While the neurostimulation treatments are procedures, and thus not regulated by the FDA, any medical devices, drugs, and/or tests used as part of this procedure may be subject to FDA regulation.

VNS: There are several devices FDA approved for vagal nerve stimulation under the product code LYJ (Stimulator, Autonomic Nerve, Implanted for Epilepsy) in the Premarket Approval Database on the FDA website. tVNS devices are not currently FDA approved for the treatment of epilepsy.

DBS: Medtronic Inc's (Minneapolis, MN) Activa Deep Brain Stimulation Therapy Systems are the only FDA approved DBS system for patients with refractory epilepsy. These devices can be found in the Premarket Approval database under the product code MBX (Stimulator, thalamic, epilepsy, implanted) and PMA number P960009.

RNS: NeuroPace Inc's (Mountain View, CA) NeuroPace RNS System is the only FDA approved RNS system for patients with refractory partial epilepsy. It received Premarket Approval in November 2013 under the product code PFN (Implanted brain stimulator for epilepsy) and PMA number P100026.

COVERAGE POLICY

Vagus Nerve Stimulation (VNS)

The *insertion* of an implantable vagus nerve stimulator may be **considered medically necessary** for patients with medically refractory focal seizures when ALL the following clinical criteria with documentation are met:

1. Member is at least 4 years or older
2. Diagnosis of ONE of the following:
    a. Focal onset or generalized onset seizures
    b. Lennox-Gastaut syndrome
3. Seizures refractory to at least one year of two or more antiepileptic medications, despite therapeutic dosing and member compliance to the medication regimen
4. Member has continued seizures, which have a major impact on activities of daily living
5. Member is ineligible for OR has failed resective surgery
6. Absence of ALL the following contraindications:
    a. Diagnosis of a progressive metabolic or degenerative disorder that will result in continued deterioration (e.g., malignant brain neoplasm or Rasmussen's encephalitis)
    b. Previous bilateral or left cervical vagotomy
    c. Cardiac pacemaker or implantable cardioverter defibrillator
    d. Risk factors for surgical complications such as active systemic infection, coagulation disorders (such as the use of anti-thrombotic therapies), or platelet count below 50,000

Transcutaneous VNS, also known as active auricular transcutaneous electrical nerve stimulation, is considered **experimental, investigational, and unproven** due to insufficient evidence in the peer reviewed scientific literature that prove safety and efficacy for any indication.

Deep Brain Stimulation (DBS)

The *insertion* of a unilateral or bilateral deep brain stimulation system (e.g., Medtronic's Activa DBS System) of the anterior nucleus of the thalamus may be **considered medically necessary** for patients with medically refractory focal seizures when ALL the following clinical criteria with documentation are met:

1. Member is at least 18 years or older
2. Diagnosis of focal partial onset seizures, with or without generalized seizure
3. Average of six or more seizures per month during the previous 3 months, with no more than 30 days between seizures

4. Seizures refractory to at least one year of three or more antiepileptic medications, despite therapeutic dosing and member compliance to the medication regimen

5. Member is ineligible for OR has failed resective surgery

6. Absence of ALL the following contraindications:
    a. Risk factors for surgical complications such as active systemic infection, coagulation disorders (such as the use of anti-thrombotic therapies), or platelet count below 50,000
    b. Progressive neurological or medical condition (e.g., brain tumors or neurodegenerative disease)
    c. Member is unable to properly operate the device OR Member does not have proper assistance to operate the device

Responsive Neurostimulation (RNS)

The *insertion* of a responsive neurostimulation system (e.g., NeuroPace RNS System) may be **considered medically necessary** for patients with medically refractory focal seizures when ALL the following clinical criteria with documentation are met:

1. Member is at least 18 years or older

2. Diagnosis of focal epilepsy

3. Seizures refractory to at least one year of two or more antiepileptic medications, despite therapeutic dosing and member compliance to the medication regimen

4. Comprehensive diagnostic testing identified 1 or 2 localized epileptogenic foci

5. Average of three or more disabling seizures per month over the past 3 months

6. Member is ineligible for OR has failed resective surgery

7. Absence of ALL the following contraindications:
    a. Risk factors for surgical complications such as active systemic infection, coagulation disorders (such as the use of anti-thrombotic therapies), or platelet count below 50,000
    b. Implanted medical devices that deliver electrical energy to the brain
    c. Member is unable to properly operate the device/magnet OR Member does not have proper assistance to operate the device/magnet
    d. Seizure focus that cannot be adequately localized
    e. Simple partial sensory seizures only

The *revision or replacement* of a responsive neurostimulation system (e.g., NeuroPace RNS System) (generator, leads, and/or battery) may be **considered medically necessary** when ALL the following clinical criteria with documentation are met:

1. Member meets all RNS insertion criteria (1 - 7) as stated above

2. Member's current device is no longer under warranty and cannot be repaired

SUMMARY OF MEDICAL EVIDENCE

As the need for treatment options in response to drug resistant epilepsy evolve, neurostimulation has emerged as a viable option. Research supports the assertion that the three forms of neurostimulation, vagus nerve stimulation (VNS), deep brain stimulation (DBS), and responsive neurostimulation (RNS) all result in seizure frequency reduction. While preliminary research is promising for these treatment methods, there is a lack of long term RCT data comparing both the clinical outcomes and safety profile of these treatments to conventional medical treatment for drug resistant

epilepsy. In addition to studying these therapies individually, research is emerging comparing the efficacy of the treatments against each other.

Li et al. (2024) performed a systematic review and meta-analysis to assess the efficacy and clinical characteristics of RNS and DBS in adult patients with drug-resistant epilepsy. They evaluated 55 studies (32 on DBS and 23 on RNS) including 9 RCTs (7 on DBS and 2 on RNS). A total of 1,568 adult patients (678 DBS patients and 890 RNS patients) were included. The analysis found no statistically significant differences in seizure reduction or responder rates between the two therapies. RNS demonstrated a mean seizure reduction of 61% (95% CI: 54-68%, $p > 0.05$) and a responder rate of 71% (95% CI: 64-78%, $p > 0.05$). Patients receiving DBS were generally younger than those receiving RNS (mean age of 32.9 years vs. 37.8 years, $p < 0.01$). Follow-up durations were similar, with DBS averaging 47.34 months and RNS 39.5 months. Adverse events were consistent with the known risks associated with implanted medical devices, seizures, and other epilepsy treatments, with large variabilities observed among studies, possibly due to different sample and follow-up time. Implantation related infection was one of the most common serious adverse events. RNS showed comparable adverse event rates to DBS for hemorrhage (0-10%) and infection (0-12.5%). Few patients who lost their lives were related to Sudden Unexpected Death in Epilepsy (SUDEP). Differences in patient selection criteria were highlighted as RNS is often used for localized epilepsy with one to two seizure foci, whereas DBS is suitable for multifocal or generalized epilepsy cases. Study limitations include the reliance on retrospective, non-RCT, and observational studies, providing lower levels of evidence compared to RCTs. Variations in seizure types, reporting accuracy, stimulation parameters, surgical targeting, and follow-up times introduced inconsistencies and potential biases. Additionally, factors like patient demographics and antiepileptic medication adjustments during the follow-up period were not fully accounted for, and the lack of multivariable regression analysis limited the ability to control for confounding variables. The authors concluded that both DBS and RNS are effective and safe options for reducing seizure burden in adult DRE patients, with both therapies providing viable alternatives for patients ineligible for resective epilepsy surgeries.

Haneef and Skrehot (2023) conducted a systematic review and meta-analysis to evaluate neurostimulation in generalized epilepsy with the goal of assessing which treatment modality, VNS, DBS, or RNS revealed better clinical results in those with refractory epilepsy. A total of 20 studies were included in the analysis and data was pooled using a random-effects model using the meta package in R. Sufficient data for meta-analysis were available from seven studies for VNS (n = 510) and nine studies for DBS (n = 87). Data from RNS (five studies, n = 18) were insufficient for meta-analysis. The mean (SD) follow-up durations were as follows: VNS, 39.1 (23.4) months; DBS, 23.1 (19.6) months; and RNS, 22.3 (10.6) months. Meta-analysis showed seizure reductions of 48.3% (95% confidence interval [CI] = 38.7%-57.9%) for VNS and 64.8% (95% CI = 54.4%-75.2%) for DBS ($p = .02$). The authors concluded that the use of DBS may lead to greater seizure reduction than VNS in generalized epilepsy. Results from RNS use are promising, but further research is required.

Touma et al. (2022) conducted a systematic review and meta-analysis evaluating the mean percentage of seizure frequency decrease as compared to baseline, as well as proportion of treatment responders and those with seizure freedom. Thirty studies were included, 6 of which were RCTs. At long-term follow-up (mean 1.3 years), five observational studies for VNS reported a pooled mean percentage decrease in seizure frequency of 34.7% (95% confidence interval [CI]: -5.1, 74.5). In the open-label extension studies for RNS, the median seizure reduction was 53%, 66%, and 75% at 2, 5, and 9 years of follow-up, respectively. For DBS, the median reduction was 56%, 65%, and 75% at 2, 5, and 7 years, respectively. The proportion of individuals with seizure freedom at last follow-up increased significantly over time for DBS and RNS, whereas a positive trend was observed for VNS. Quality of life (QoL) was improved in all modalities. The most common complications included hoarseness, and cough and throat pain for VNS and implant site pain, headache, and dysesthesia for DBS and RNS. The authors concluded that neurostimulation is an effective treatment for refractory epilepsy with few major complications. Seizure-reduction rates among the three therapies were similar during the initial blinded phase with promising long term follow-up studies are for RNS and DBS, however encouraging long term follow up is lacking for VNS.

Vagus Nerve Stimulation (VNS)

Randomized Controlled Trials

Klinkenberg et al. (2012) conducted a randomized controlled trial to evaluate the effects of VNS in children with intractable epilepsy on seizure frequency and severity and in terms of tolerability and safety. In this study 41 children (23 males; 18 females; mean age at implantation 11y 2mo, SD 4y 2mo, range 3y 10mo-17y 8mo) were included. Thirty-five participants had localization-related epilepsy (25 symptomatic; 10 cryptogenic), while six participants had

generalized epilepsy (four symptomatic; two idiopathic). During a baseline period of 12 weeks, seizure frequency and severity were recorded using seizure diaries and the adapted Chalfont Seizure Severity Scale (NHS3), after which the participants entered a blinded active controlled phase of 20 weeks. During this phase, half of the participants received high-output VNS (maximally 1.75mA) and the other half received low-output stimulation (0.25mA). Finally, all participants received high-output stimulation for 19 weeks. For both phases, seizure frequency and severity were assessed as during the baseline period. At the end of the randomized controlled blinded phase, seizure frequency reduction of 50% or more occurred in 16% of the high-output stimulation group and in 21% of the low-output stimulation group (p=1.00). There was no significant difference in the decrease in seizure severity between participants in the stimulation groups. Overall, VNS reduced seizure frequency by 50% or more in 26% of participants at the end of the add-on phase. The overall seizure severity also improved (p<0.001). The authors concluded that VNS is a safe and well-tolerated adjunctive treatment of epilepsy in children. Our results suggest that the effect of VNS on seizure frequency in children is limited. However, the possible reduction in seizure severity and improvement in well-being makes this treatment worth considering in individual children with intractable epilepsy.

Systematic Reviews and Meta-Analyses

Melese et al. (2024) completed a systematic review to determine how VNS affected patients with drug-resistant epilepsy's quality of life, cognitive abilities, and seizure outcomes. The review encompassed eleven studies, consisting of two randomized controlled trials, four prospective studies, two retrospective studies, and three experimental studies. Participants' ages averaged between 11 and 33 years. The total sample size included 712 individuals diagnosed with drug-resistant epilepsy, all of whom had a vagus nerve stimulator implanted in their left neck following a diagnosis of refractory epilepsy. Follow-up periods varied from 6 to 36 months. Patients were categorized as good responders to VNS therapy if they experienced at least a 50% reduction in seizure frequency, while those with less than a 50% reduction were considered poor responders. The pooled seizure reduction rate among these patients was 56.94%, with individual study rates ranging from 48.90% to 83.00%. VNS not only improved seizure control but also enhanced the quality of life for patients with drug-resistant epilepsy, with potential benefits for mood and cognitive symptoms. The review suggests that VNS may be beneficial for individuals with drug-resistant epilepsy. The review indicates that VNS therapy can be advantageous for patients dealing with drug-resistant epilepsy, particularly in terms of reducing seizure frequency and improving their overall quality of life. Additionally, there may be potential benefits for mood and cognitive symptoms as well. However, the review had limitations, including the small sample size of 11 studies, which precluded meta-regression analysis. Additionally, there was clinical heterogeneity across the studies due to variations in treatment methods, patients' underlying conditions, center experience with VNS, treatment duration, and stimulation parameters. Some studies also had a moderate-to-high risk of bias.

Panebianco et al. (2022 & 2015) conducted a systematic review and meta-analysis on VNS for focal seizures. The 2022 analysis focused on reviewing the literature to update the conclusions made in the 2015 analysis; however, the authors did not identify any new studies for the update, therefore the conclusions made in the 2015 analysis remain unchanged. The 2015 analysis included randomized, double-blind, parallel or crossover studies, controlled trials of VNS as add-on treatment comparing high and low stimulation paradigms (including three different stimulation paradigms - duty cycle: rapid, mid, and slow) and VNS stimulation versus no stimulation or a different intervention in patients with drug resistant partial seizures that were not eligible or had failed surgical interventions. Five 5 studies were analyzed for a total of 439 patients. The two primary outcomes assessed were: 50% or greater reduction in total seizure frequency, and adverse effects. Pooled Risk Ratios with 95% confidence intervals (95% CI) were estimated for outcomes of seizure frequency and adverse effects. The overall risk ratio (95% CI) for 50% or greater reduction in seizure frequency across all studies was 1.73 (1.13 to 2.64) showing that high frequency VNS was over one and a half times more effective than low frequency VNS. The risk ratios of adverse effects were as follows: voice alteration and hoarseness 2.17 (99% CI 1.49 to 3.17); cough 1.09 (99% CI 0.74 to 1.62); dyspnea 2.45 (99% CI 1.07 to 5.60); pain 1.01 (99% CI 0.60 to 1.68); paresthesia 0.78 (99% CI 0.39 to 1.53); nausea 0.89 (99% CI 0.42 to 1.90); headache 0.90 (99% CI 0.48 to 1.69). The authors concluded VNS for partial seizures appears to be an effective and well tolerated treatment and using the high stimulation was significantly better than low stimulation in reducing frequency of seizures. Further high-quality research is needed to validate these findings.

Transcutaneous Vagal Nerve Stimulation (t-VNS)

Randomized Controlled Trials

Yang et al. (2023) conducted a randomized, double-blind, controlled trial to evaluate the effectiveness and safety of t-VNS as a treatment for epilepsy. The primary goal was to show the superiority of t-VNS as an add-on therapy over a control group in reducing seizure frequency over a 20-week period. The study also examined the impact of t-VNS on

patients' quality of life, mood, and cognitive function. T-VNS is a newly developed therapy aimed at addressing the limitations of invasive vagus nerve stimulation. A total of 150 patients were randomly assigned to either the active stimulation group or the control group. Demographic information, seizure frequency, and adverse events were documented at the start of the study and at 4, 12, and 20 weeks of stimulation. At the 20-week mark, patients were evaluated using the quality-of-life assessment, the Hamilton Anxiety and Depression scale, the MINI suicide scale, and the MoCA scale. Seizure frequency was tracked based on the patients' seizure diaries, and a reduction in seizure frequency greater than 50% was considered effective. On average, seizure frequency in the active stimulation group dropped significantly by 30.75% over the course of the 20-week t-VNS treatment, which exceeded the reduction observed in the control group. The study had several limitations: a small sample size, dropout rate of 25.3%, a focus on seizure frequency without assessing seizure severity; incomplete EEG data, and potential inaccuracies in seizure frequency measurement from using seizure diaries. The study demonstrated that t-VNS is a safe and effective therapy for epilepsy, with no significant differences in adverse events between the active and control groups, and no severe adverse events reported. Key adverse events included pain, sleep disturbance, flu-like symptoms, and local skin discomfort. While the study did not show significant improvements in quality of life, mood, or cognitive state, it highlighted t-VNS as a promising noninvasive treatment for patients resistant to anti-seizure medications, warranting further validation in future research.

Systematic Reviews and Meta-Analyses

Lampros et al. (2021) conducted a systematic review on t-VNS in the treatment of epilepsy. Ten studies were included in the analysis for a total of 350 patients across all studies. The frequency of which t-VNS was applied varies across the studies from 10-30Hz, and treatment intensity was usually adjusted according to patients' preferences and pain tolerance (around 1mA). The reviewed clinical trials produced a mean seizure frequency reduction from 30 to 65 percent. Three studies reported a statistically significant (p<0,05) improvement in patients' quality of life and two studies reported statistically significant (p<0,05) seizure severity reduction. The most common side effect was headache (8.9%), skin irritation at the placement site (7.1%) and nasopharyngitis (5.1%). No serious adverse events were reported in any study. The authors concluded that the available studies analyzed were too heterogenous to extrapolate a conclusion on t-VNS's safety and efficacy, and therefore could only offer a possible benefit to patients with refractory seizures.

Deep Brain Stimulation (DBS)

Randomized Controlled Trials

Herrman et al. (2019) conducted a prospective, randomized, double-blind evaluation of the safety and efficacy of DBS for adult patients with focal refractory epilepsy, with or without subsequent generalization, who were not candidates for resective surgery (N = 18). In the three months preceding to implantation, participants experienced an average of 53 seizures per month and had taken an average of 13 anticonvulsant medications (range: 5 to 15). The exclusion criteria were identical to those used in the Stimulation of the Anterior Nuclei of Thalamus for Epilepsy (SANTE) study (Fisher et al., 2010). Participants were randomized after DBS device implantation to receive 5-volt stimulation through the devices (intervention, N = 8) or no stimulation (control, N = 10) for a 6-month blinded period. During the nonblinded open-label phase (months 7 through 12), all subjects received 5-volt stimulation; data obtained at 3, 6, 9, and 12 months focused on seizure frequency, seizure type, and adverse effects. The duration of this study was 12 months; however, participants received their randomized treatment for only the first six months. For the second six-month period, all participants got active treatment. At the conclusion of the blinded six-month period, the authors found no statistically significant changes between groups. During the open active vs therapy phase at 6-12 months, there was a 22% decrease in the frequency of all seizures compared to baseline (p=0.009). At the 12-month time point, four participants experienced a reduction in total seizure frequency of 50%, and five subjects experienced a reduction in focal seizure frequency of 50%. There was no evidence of a cumulative effect. LSSS at 6 months showed no significant differences between groups, however a slight, significant drop in LSSS was observed after all subjects had received stimulation for 6 months.

- Hermann et al. (2022) and Heminghyt et al. (2202) reported on the twelve-month results of the randomized controlled trial evaluating the cognitive impacts of ANT-DBS in the treatment of refractory epilepsy. The participants were assessed via 22 neuropsychological assessments at baseline, at six months, and at one year post implantation. There were no significant group differences in cognitive change between baseline and six months, patients reported fewer symptoms of executive dysfunction in the group who had a full 12 months of stimulation. Patients showing significant improvement in seizure frequency had better performance in a measure of verbal learning. The authors concluded the results indicate that ANT-DBS has limited effects on cognitive functioning, as measured by formal tests after 6- or 12-month stimulation; but may have a positive influence on

executive function. The findings provide limited support for an association between seizure frequency and cognitive functioning.

Fisher et al. (2010) published the findings of a multicenter, RCT of bilateral SANTE trial. Prior to entering in the study, individuals had failed trials of at least three antiseizure drugs and had documented at least 6 seizures per month in a 3-month daily epileptic diary, but no more than 10 seizures per day. Participants were randomly assigned to one of two groups: stimulation on or stimulation off. The study implanted Medtronic DBS devices with electrodes in the ANT in 109 adult patients (n = 109) with medically refractory partial seizures, including secondarily generalized seizures. The trial was structured with a 3-month double-blinded phase, with a subsequent 9-month open-label follow-up period, with an additional data collection follow-up at 2, 3, 4, 5, and 7 years. Individuals in the intervention group received 5 volts with 145 pulses per second stimulation, with 1 minute on and 5 minutes off stimulation (intervention, N = 54); participants in the control condition received no stimulation during the 3-month blinded phase of the study (control, N = 54). Patients who received stimulation therapy reported a 29% greater reduction in seizure frequency compared with sham stimulation at three months and 54% of patients had a seizure reduction of at least 50% by two years in the unblinded phase. Complex partial seizures and "most severe" seizures were the most drastically reduced. Participants in the stimulated group reported higher depression (15 versus 2%), memory difficulties (13 versus 2%), as well as 14 implant site infections (13%), and five asymptomatic hemorrhages (5%). According to the authors, DBS of the anterior nuclei was mostly palliative in this population, but 14 participants (12.7%) were seizure-free for at least 6 months. Furthermore, significant improvements were observed in some subjects who had previously been unaided by multiple medications, VNS, or epilepsy surgery. It was concluded that “Additional clinical experience may help to establish the best candidates and stimulation parameters, and to further refine the risk–benefit ratio of this treatment.”

Results from the SANTE double-blinded phase and the open-label follow-ups were reported in 3 publications (Salanova et al. 2015; Troster et al. 2017; Salanova et al. 2021)

- Salanova et al. (2015) in a long-term follow-up study of the same trial which began 13 months following device implantation, participants receiving active stimulation were followed for an additional 4 years. The results show a decrease in seizures and an improvement in quality of life over time. The median percent seizure reduction from baseline at 1 year was 41%, and 69% at 5 years. The responder rate (greater than or equal to 50% reduction in seizure frequency) at 1 year was 43%, and 68% at 5 years. In the 5 years of follow-up, 16% of subjects were seizure-free for at least 6 months. It is noted that by the 5-year follow-up, 61 participants with active DBS implants had begun taking at least 1 new antiseizure drug that they had not taken at baseline. There were no unexpected adverse effects reported. Depression, suicidality, and SUDEP rates were comparable to those with general refractory epilepsy. The results of this study show that DBS has a significant long-term benefit for epileptic patients; however, the sample size was small, and the study was not blinded. Additional data from larger, blinded RCTs is necessary.
- Troster et al. (2017) assessed incidence of memory and depression adverse events in the SANTE Trial blinded phase and their relationship to objective neurobehavioral measures, baseline characteristics, quality of life, and long-term neurobehavioral outcome. The neurobehavioral adverse events and neuropsychological data from the SANTE Trial were analyzed. A seven-year follow-up with 67 of the participants reported no statistically significant change in depression, anxiety, or memory between measure collection at baseline and 7 years after implantation. The authors concluded that, in a small number of patients, bilateral ANT DBS was associated with subjective depression and memory adverse events during the blinded phase, but not with objective, long-term neurobehavioral worsening. Monitoring and neuropsychological assessment of depression and memory are recommended from a theoretical standpoint, as well because the active stimulation group experienced more memory and depression adverse events than the control group.
- Salanova et al. (2021), in a subgroup analysis with the 50 remaining participants at the 7-year follow-up, found that participants with and without prior vagal nerve stimulation (VNS) did not have significantly different median seizure reductions (median for group with VNS, 75%; N = 21; median for group without prior VNS, 78%; N = 29; between-group difference, p > .05). Participants at the 7-year follow-up with temporal lobe seizures reported a significant median seizure reduction of 78% (N = 35) compared to baseline; participants with frontal lobe seizures reported a nonsignificant median reduction of 86% (N = 9) compared to baseline; and participants with seizures in other regions reported a significant median reduction of 39% (N = 11) compared to baseline. The authors reported that the improvement in seizure severity score on the Liverpool Seizure Severity Scale (LSSS) found at 5 years remained stable (no statistics reported). By the 7-year follow-up, 77% of the 50 remaining participants had added at least 1 new antiseizure drug, and the authors reported that the trajectory of improvement in seizure frequency was similar between participants with and without added antiseizure drugs (no statistics reported).

Responsive Neurostimulation (RNS)

Randomized Controlled Trials

Nair et al. (2020) conducted The Long-Term Treatment (LTT) study evaluating the long-term safety and efficacy of the RNS system as an adjunctive therapy for reducing seizure frequency in adults with partial onset seizures resistant to at least two antiepileptic medications. The study spanned a 7-year open-label phase following the completion of participants' initial 2-year feasibility or pivotal studies, providing a total of up to 9 years of follow-up data, with 230 participants included in the LTT phase after completing the prior studies. The study was a single-group assignment, open-label study where participants continued their epilepsy medications alongside the implanted RNS system. Data collection occurred at 6-month intervals for safety and efficacy, and annually for quality of life. Primary measures included the assessment of serious adverse events from two to nine years post-implantation and the percentage reduction in seizure frequency compared to pre-implantation baseline levels, with data collected at six-month intervals. Secondary outcomes examined the proportion of participants achieving a ≥ 50% reduction in disabling seizures (the responder rate), overall improvements in QoL as measured by Quality of Life in Epilepsy Inventory-89 (QOLIE-89) or QOLIE-31P scores, and the rate of all adverse events occurring throughout the study. The findings from the study highlighted significant and progressive seizure reductions, with the median frequency of seizures decreasing by 75% by year nine (NeuroPace 2019). At 9 years, responder rate was 73%, 35% had a ≥ 90% reduction in seizure frequency, and 18.4% experienced ≥ 1 year of seizure freedom, with 62% seizure-free at the last follow-up and an average seizure-free period of 3.2 years (range 1.04-9.6 years). Overall QoL and epilepsy-targeted and cognitive domains of QOLIE-89 remained significantly improved ($p < 0.05$) (Nair et al. 2020). Adverse events were primarily surgical or device-related, with 12.1% of participants experiencing implantation site infections, most of which involved superficial soft tissue and required explantation in 16 cases. Non-seizure related intracranial hemorrhages occurred in 2.7% of participants, typically resolving without neurologic sequelae. Depression and suicidality were reported in 9.8% of patients, primarily among those with preexisting histories of these conditions. SUDEP rates were significantly lower than expected for comparable populations, with a combined rate of 2.8 per 1,000 patient-stimulation years. Notably, seizure related adverse events including status epilepticus, occurred at rates consistent with the underlying epilepsy population and were rarely attributed to the device (Bergey et al. 2015; Heck et al. 2014; Nair et al. 2020; NeuroPace 2019).

Morrell (2011) reported on the pivotal study which assessed the safety and efficacy of RNS System for patients with drug-resistant and focal onset epilepsy. The two-year multicenter, double-blind, RCT of 191 adults (n = 191) with refractory focal seizures with or without secondary generalization (RNS System in Epilepsy Study Group). Participants were adults (18-70 years of age), had focal onset seizures that were left uncontrolled in ≥2 trials of antiepileptic drugs, suffered 3≥ disabling seizures per month on average, and had up to two epileptogenic regions. Of those enrolled, 32% had prior epilepsy surgery and 34% previously had VNS, which was turned off or explanted before enrollment. All participants had the RNS implantation procedure but were randomly assigned to activated and nonactivated groups and followed for the 12-week blinded treatment phase, then an 84-week open-label period where all subjects received active therapy. After a 4-week period during which no patients' systems were activated to control for any temporary insertion effect, those in the activated group had RNS activated for 12 weeks. After the initial 12 weeks all patients' systems were activated, and patients were followed on an open-label basis. The responder rate (percentage of subjects with a ≥ 50% reduction in seizures) over the blinded period was not significant overall, with 29% in the treatment group responding vs. 27% in the sham group. However, seizure-free days over the first month continued to increase in the treatment group but declined for the sham group. By the third month, the treatment group had 27% fewer days with seizures vs. 16% fewer days in the sham group ($p=0.048$). The difference between the two groups had widened at 5 months after implantation with disappearance of the lesioning effect. The reduction rate in seizure frequency was significantly better in patients receiving stimulation by the RNS System than in the sham group (41.5% vs 9.4%, $p = 0.008$). The serious adverse event rate for medical and surgical events for the first 84 weeks was 18.3%. The authors concluded that this pivotal RCT presents Class I evidence that responsive cortical stimulation is effective in reducing the frequency of disabling partial onset seizures that were refractory to antiepileptic drugs and, in many cases, vagus nerve stimulation or epilepsy surgery.

- Heck et al. (2014) published the final 2-year results of the pivotal trial. The active group had a -37.9% change in seizures and the sham group had a -17.3% change ($p=0.012$) at the end of the blinded period. In the open-label period, the median percent reduction in seizures was 44% at 1 year and 53% at 2 years, indicating a progressive and significant improvement over time. The authors found no differences in the rate of serious adverse events between groups, which was consistent with the known risks of an implanted medical device, seizures, and other epilepsy treatments. No adverse events on neuropsychological function or mood were observed.

Systematic Reviews and Meta-Analyses

Mushtaq et al. (2024) performed a systematic review and meta-analysis to assess the efficacy, safety, and QoL impacts of RNS for drug-resistant epilepsy. They assessed five studies published between 2015-2023, including two systematic reviews and meta-analyses (Kusyk et al. 2022) (Touma et al. 2022), and one RCT. Across the studies, RNS demonstrated consistent effectiveness in reducing seizure frequency, with median reductions ranging from 54% to 75% over time in long term-analyses. Mean responder rates (≥50% reduction in seizure frequency) were approximately 68% (95% CI: 60%-75%). QoL improvements were reported in 44% of participants in one randomized controlled trial using the QOLIE-89 scoring manual, a validated tool used to evaluate QoL across 17 primary scales and four composite subscales (epilepsy targeted, cognitive, mental health, and physical health). RNS complication rates varied between studies, with device related infections being the most common, occurring in approximately 8-19% of cases. The systematic review highlights variability in outcomes based on patient characteristics, epilepsy type, and study design. The methodological variability among studies, such as differences in patient selection criteria and stimulation parameters, limits generalizability. Other limitations include small sample sizes, short follow-up periods, and potential publication bias favoring positive outcomes. The authors concluded RNS to be a viable treatment option for patients with drug-resistant epilepsy, offering substantial improvements in seizure control and QoL with a manageable safety profile. Future studies are necessary to optimize patient selection, refine treatment protocols, and ensure sustained therapeutic benefits over time.

National and Specialty Organizations

The **American Academy of Neurology (AAN)** evidence-based guideline on VNS for the treatment of epilepsy indicates that VNS may be considered for seizures in children, for Lennox-Gastaut syndrome (LGS) associated seizures, and for improving mood in adults with epilepsy (Level C). VNS may be considered to have improved efficacy over time (Level C). Children should be carefully monitored for site infection after VNS implantation (Morris et al. 2013, reaffirmed 2022).

The **American Society for Stereotactic and Functional Neurosurgeons (ASSFN)** guidelines state neuromodulation treatments including DBS expand the surgical options for epilepsy patients and provide options for patients who are not candidates for resective surgery. It notes that DBS of the bilateral ANT is an FDA approved, safe and efficacious treatment option for patients with refractory focal epilepsy (Gummadavelli 2022).

The **National Institute for Health and Care Excellence (NICE)** published the following guidelines:

- *Epilepsies in children, young people and adults* (NICE 2022) stating that vagal nerve stimulation in treating refractory epilepsy in children and adults is appropriate in the setting of drug-resistant seizures and considers VNS an adjunctive therapy.
- *DBS guidance for patients with refractory epilepsy* (NICE 2020) stating that due to the limited quantity and quality of published evidence, the recommendations are that individuals with refractory epilepsy and anterior thalamic targets should only undergo DBS under special arrangements for clinical governance, consent, audit, and research. NICE recommends special arrangements when the independent advisory committee determines that there is ambiguity about the safety and effectiveness of certain procedures.

The **Washington State Health Authority (WSHA)** published a report in 2020 entitled *Vagal Nerve Stimulation for Epilepsy and Depression* in April 2020. The final evidence report states that "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."

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
61850	Twist drill or burr hole(s) for implantation of neurostimulator electrodes, cortical
61860	Craniectomy or craniotomy for implantation of neurostimulator electrodes, cerebral, cortical

61863	Twist drill, burr hole, craniotomy or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; first array
61864	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), without use of intraoperative microelectrode recording; each additional array (List separately in addition to primary procedure)
61880	Revision or removal of intracranial neurostimulator electrodes
61867	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; first array
61868	Twist drill, burr hole, craniotomy, or craniectomy with stereotactic implantation of neurostimulator electrode array in subcortical site (e.g., thalamus, globus pallidus, subthalamic nucleus, periventricular, periaqueductal gray), with use of intraoperative microelectrode recording; each additional array (list separately in addition to primary procedure)
61880	Revision or removal of intracranial neurostimulator electrodes
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	Open 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
95836	Electrocorticogram from an implanted brain neurostimulator pulse generator/transmitter, including recording, with interpretation and written report, up to 30 days
95970	Electronic analysis of implanted neurostimulator pulse generator/transmitter (e.g., contact group(s), interleaving, amplitude, pulse width, frequency [Hz], on/off cycle, 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 brain, cranial nerve, spinal cord, peripheral nerve, or sacral nerve neurostimulator pulse generator/transmitter without programming
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
95983	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 brain neurostimulator pulse generator/transmitter programming, first 15 minutes face-to-face time with physician or other qualified health care professional
95984	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 brain neurostimulator pulse generator/transmitter programming, each additional 15 minutes face-to-face time with physician or other qualified health care professional (List separately in addition to code for primary procedure)
0783T	Transcutaneous auricular neurostimulation, set-up, calibration, and patient education on use of equipment
0908T	Open implantation of integrated neurostimulation system, vagus nerve, including analysis and programming, when performed
0909T	Replacement of integrated neurostimulation system, vagus nerve, including analysis and programming, when performed
0910T	Removal of integrated neurostimulation system, vagus nerve
0911T	Electronic analysis of implanted integrated neurostimulation system, vagus nerve; without programming by physician or other qualified health care professional
0912T	Electronic analysis of implanted integrated neurostimulation system, vagus nerve; with simple programming by physician or other qualified health care professional

HCPCS (Healthcare Common Procedure Coding System)

Code	Description
C1767	Generator, neurostimulator (implantable), non-rechargeable
C1778	Lead, neurostimulator (implantable)
C1787	Patient programmer, neurostimulator
C1820	Generator, neurostimulator (implantable), with rechargeable battery and charging system
C1822	Generator, neurostimulator (implantable), high frequency, with rechargeable battery and charging system
L8679	Implantable neurostimulator, pulse generator, any type
L8680	Implantable neurostimulator electrode, each
L8681	Patient programmer (external) for use with implantable programmable neurostimulator pulse generator, replacement only
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, replacement only
L8695	External recharging system for battery (external) for use with implantable neurostimulator, replacement only

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

02/12/2025 New policy due to combination of prior separate VNS (MCP 006), DBS (MCP 335), and RNS (MCP 430) policies. IRO Peer Review on February 3, 2025, by a practicing, board-certified physician with a specialty in Neurology.

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