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ASSFN Position Statement on Deep Brain Stimulation for Medication-Refractory Epilepsy

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Neuromodulation has taken a foothold in the landscape of surgical treatment for medically refractory epilepsies and offers additional surgical treatment options for patients who are not candidates for resective/ablative surgery. Approximately one third of patients with epilepsy suffer with medication-refractory epilepsy. A persistent underuse of epilepsy surgery exists. Neuromodulation treatments including deep brain stimulation (DBS) expand the surgical options for patients with epilepsy and provide options for patients who are not candidates for resective surgery. DBS of the bilateral anterior nucleus of the thalamus is an Food and Drug Administration-approved, safe, and efficacious treatment option for patients with refractory focal epilepsy. The purpose of this consensus position statement is to summarize evidence, provide recommendations, and identify indications and populations for future investigation in DBS for epilepsy. The recommendations of the American Society of Functional and Stereotactic Neurosurgeons are based on several randomized and blinded clinical trials with high-quality data to support the use of DBS to the anterior nucleus of the thalamus for the treatment of refractory focal-onset seizures.

KEY WORDS: Deep brain stimulation, Thalamus, Epilepsy, Neuromodulation

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EXECUTIVE SUMMARY

Background and Purpose of Statement

- Neuromodulation has taken a foothold in the landscape of surgical treatment for medically refractory epilepsies and offers additional surgical treatment options for patients who are not candidates for resective/ablative surgery.
- Deep brain stimulation (DBS) of the bilateral anterior nucleus of the thalamus (ANT) is an Food and Drug Administration (FDA)-approved, safe, and efficacious treatment option for patients with refractory focal epilepsy.
- Our goal is to summarize evidence, provide recommendations, and identify indications and populations for future investigation in DBS for epilepsy.

Importance of the American Society of Stereotactic and Functional Neurosurgery Statement

- Stereotactic and functional neurosurgeons are involved in the care of patients with medically refractory epilepsies and are domain-specific experts in the procedures (and related risks, benefits, and alternatives) of DBS.
- Clinical practice parameter published jointly by the American Academy of Neurology, American Epilepsy Society, and American Association of Neurological Surgeons (2003) recommends early referral of patients with medically refractory epilepsy to a tertiary epilepsy center for surgical evaluation.

Importance and Underutilization of Epilepsy Surgery in the Treatment of Refractory Epilepsy

- Approximately one third of patients with epilepsy suffer with medication-refractory epilepsy.
- A persistent underuse of epilepsy surgery exists.
- Neuromodulation treatments including DBS expand the surgical options for patients with epilepsy and provide options for patients who are not candidates for resective surgery.

Indications for DBS for Medication-Refractory Epilepsies

- Confirmed diagnosis of epilepsy by an epileptologist with focal-onset seizures, with or without generalization;

- Failure to adequately control seizures after 2 (or more) appropriate and adequately dosed antiseizure medications;
- Either partial-onset seizures with a localized onset in a region not amenable to resection or after failed resective surgery or focal-onset seizures with a distributed or unclear onset zone.

Contraindications With DBS for Medically Refractory Epilepsies

- Patients who are anticipated to require transcranial magnetic stimulation (TMS) therapy in the future because TMS therapy is contraindicated for patients with an implanted DBS system.
- Patients who are unable or do not have the necessary assistance to properly operate the DBS therapy, patient programmer or charging system where applicable.
- Patients in whom the risk of an intracranial surgical procedure and/or general anesthesia is unacceptable because of an underlying medical condition.

Support for Recommendations

Several randomized and blinded clinical trials support the use of DBS for the treatment of refractory epilepsy with high-quality data to support the use of DBS to the ANT for the treatment of refractory focal-onset seizures.

SUPPORTING LITERATURE

Background

Epilepsies are common, chronic, heterogenous, and debilitating syndromes. The lifetime prevalence of epilepsy is 1% worldwide,[1] and 30% to 40% of patients suffer medically refractory epilepsy (as defined as resistant to 2 or more appropriate first-line and patient-tolerated antiseizure medications).[2,3] Epilepsies presenting with partial/focal-onset seizures, especially those associated with temporal lobe epilepsy, are over-represented among drug-resistant epilepsy.[4] The sudden and unpredictable occurrence of seizures leads to significant morbidity, mortality, and impairment to quality of life.[5,6] Surgical treatment should be considered early in medically refractory epilepsy.[7]

Surgical Treatment of Medically Refractory Epilepsy

The surgical treatment paradigm for epilepsy syndromes is first to aim for complete or partial resection or ablation of the seizure-onset zone if this can be performed safely without significant neurological or neuropsychological impairment. Anterior temporal lobectomy has been shown to be highly efficacious for temporal lobe epilepsy in a prospective randomized controlled trial (RCT),[8] with 58% freedom from seizures with an altered level of consciousness (Engel I status) after 1 year in the surgical group compared with 8% with continuous medical therapy. Long-term follow-up suggests that[7] 50% to 60% of patients with temporal lobe epilepsy obtain Engel I status,[9,10] whereas resective outcomes after extratemporal-onset zones are less favorable at 40% to 50%.[11-13] Recently, laser interstitial thermocoagulation therapy has been used as an ablative strategy for mesial temporal epilepsy (50%-60% 1-year seizure freedom[14,15]) and epilepsies originating from deep onset focus (ie, hypothalamic hamartomas and deep focal cortical dysplasias).[16,17]

For people suffering from medically refractory epilepsy who are not candidates for resection or ablation, neuromodulation is an established treatment. Large randomized studies of vagus nerve stimulation (VNS) found 24.5% to 28% reduction in seizure frequency[18,19]; long-term follow-up showed that 44.1% of patients had >50% long-term reduction in seizure frequency.[20] Responsive neurostimulation (RNS), which is distinct because of its closed-loop "response" to an electrographically detected seizure, has been shown in the pivotal RCT to have a 37.9% decrease in seizure frequency in a 12-week blinded period.[21] Long-term follow-up showed a 53% seizure reduction after a 2-year open-label period,[22] with long-lasting efficacy and even progressive median seizure reduction (75% reduction at 9 years).[23] Of note, for patients with a VNS or RNS device currently in place, that device does not need to be removed before a DBS system is placed.[24]

ANT—DBS

The ANT is composed of 3 subnuclei and is a highly connected key node in several networks, including the Papez circuit, through connections to the subiculum, retrosplenium, mammillary bodies, orbitofrontal prefrontal cortex, and anterior cingulate cortex.[25] ANT was thought to be a suitable target given its wide connections throughout the brain, especially with those circuits related to epilepsy.

The pivotal multicenter double-blind RCT of stimulation of the anterior nucleus of the thalamus in epilepsy (SANTE) included 110 adult patients with medically refractory (failing greater than 2 antiepileptic drugs), partial-onset epilepsy.[26] Sixty percent of patients had temporal-onset seizures, 27.3% had frontal-onset, and remainder of seizure onsets included diffuse/multifocal/others (18.2%), parietal (4.5%), and occipital (4.5%). The main clinical end points were safety as defined by adverse events/sudden unexpected death in epilepsy events and efficacy as defined by the seizure rate between active and control stimulations using generalized estimating equations. Secondary end points were responder (>50% seizure reduction) rate, seizure-free interval, mean percentage of seizure-free days, and treatment failure rate. Quality of life was also measured (using QOLIE-31), as well as neuropsychological testing, rescue medication use, and healthcare resources utilization. Subjects had an average of 6 or more partial-onset seizures per month and were refractory to at least 3 antiepileptic drugs. The parallel-arm study design was as follows: 3-month baseline phase, 1-month operative, 3-month blinded, 9-month unblinded, and long-term follow-up (Figure). When patients were randomized in a 1:1 fashion, investigators observed a 17% decrease in total seizure rate in the blinded active (5 V) vs control (0 V) groups by post hoc analysis (P = .045) and a 38%

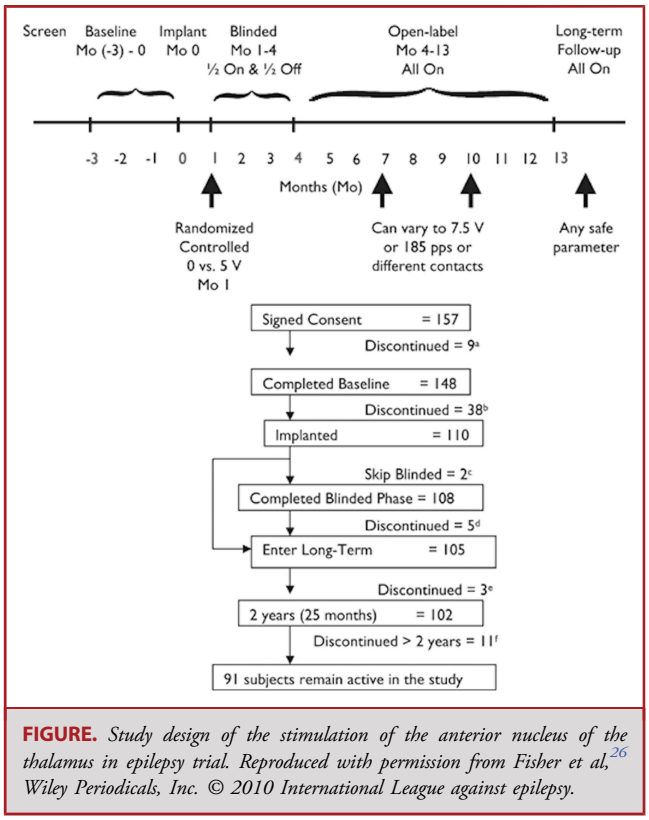

FIGURE. *Study design of the stimulation of the anterior nucleus of the thalamus in epilepsy trial. Reproduced with permission from Fisher et al,[26] Wiley Periodicals, Inc. © 2010 International League against epilepsy.*

decrease in median seizure frequency at 3 months of active stimulation compared with 14.5% with sham stimulation. Across the entire blinded phase, the median seizure frequency was decreased by 35% with active stimulation and 21.1% with control stimulation (P = .119). Four months after DBS implantation, all patients had active stimulation with programing restrictions and antiepileptic drugs stability as an open-label unblinded phase (3-9 months after implant). There were no such restrictions in longer-term follow-up in the past 9 months after implant. Seizure frequency was progressively reduced with a longer duration of use; median seizure frequencies for years 1 to 7 were as follows: −41.1%, −55.6%, −52.9%, −65.9%, −69.4%, −74.9%, and −74.8%. At 2 years of open-label use, 53.7% of patients had >50% decrease in seizure frequency ("responders"),[26] 67.8% responder rate was observed after a total of 5 years of open-label use,[27] and at 7 years, 74% of patients were responders.[27] Quality of life as measured by the Liverpool Seizure Severity Score and QoLIE-31 showed statistically-significant and clinically-meaningful improvement carrying out to 5 years of ANT stimulation.[27] The SANTE trial and its follow-up results are notable in the context of their low dropout rate, with 75 of 110 implanted subjects remaining active beyond 5 years.[27]

A smaller RCT, designed in the same manner as SANTE, performed in 18 patients with severe and refractory forms of epilepsy (averaging 43.5 impaired awareness and 9.6 generalized tonic-clonic seizures per month) from a single center showed a 21% decrease in frequency of focal seizures with impaired awareness from baseline rates in active stimulation compared with baseline (P = .038), but not significant compared with the control stimulation group, in a 6-month blinded phase. When both groups were stimulated for 6 months in an unblinded phase, a combined 20% decrease in seizure frequency from baseline was observed (P = .009).[28] It was terminated early because of the lack of the beneficial effect. Limitations of the study included small sample sizes and short period of observation.

On the basis of these studies, including the long-term follow-up, the FDA approved ANT DBS for the treatment of focal-onset epilepsy with or without secondary generalization in 2018.[29]

Safety of DBS Surgery

Although DBS is an invasive procedure, extensive collective experience and follow-up with DBS, including its long history of use in movement disorders, have shown it to be very safe. The predominant risks are surgical site infections (9%-12%) and intracranial hemorrhage (1.6%-3.7%).[30] Less adverse risks include lead migration (1.6%) or fracture (1.5%), skin erosion (0.48%), paresthesias, and generator malfunction.[31] Rarely reported complications include wire-tethering strictures,[32] aborted procedures, or deaths. Potential complications specific to anterior thalamic nucleus DBS, discussed further below, include possible worsening of a mood disorder or depression.

Systematic Reviews

Multiple literature reviews of RCTs and case series regarding DBS for epilepsy show a steady increase in the use of DBS as a neurostimulation strategy and support its use for medically refractory epilepsy.[33-39] Previous systematic reviews have noted the lack of studies with direct comparisons between neurostimulation strategies.[40] Three rigorous systematic reviews of interest support the use of ANT DBS in medically refractory epilepsy. Chambers and Bowen[41] evaluated 11 studies regarding electrical stimulation for medically-refractory epilepsy, including 6 RCTs for DBS and VNS. They noted the reduced seizure frequency with ANT DBS, especially with long-term use. The authors did not comment on the potential reporting bias because seizure reporting is reliant on self-reporting and risk of publication bias based on incomplete reporting of all outcomes. The Cochrane Group performed a systematic review of 12 RCTs of neurostimulation for refractory epilepsies including DBS and RNS.[30] Based on the SANTE RCT, they concluded that ANT DBS was safe and well tolerated, with high-quality evidence suggesting that 3 months of ANT DBS reduced seizure frequency, despite the potential reporting bias. They noted no significant impact on seizure freedom or responder rate.[30] Boon et al[42] included a systematic review of all available invasive and noninvasive neurostimulation techniques (including VNS, DBS, RNS, transcranial direct current stimulation, transcutaneous VNS, TMS, and trigeminal nerve stimulation). For ANT DBS, they evaluated the SANTE RCT and the 2 previous systematic reviews; they summarized the previous reviews

as suggesting low-moderate quality evidence for the safety and efficacy of ANT DBS for refractory epilepsies. Added review of literature suggested no contraindications to ANT DBS except to caution the potential increase in self-reported mood or memory issues.

Noncomparative Studies

Numerous open-label studies and case series since the first human reports for ANT DBS in the 1980s[43] show efficacy ranging from 24% to 90% seizure frequency reduction in generalized, focal, and secondarily generalized seizures (previously reviewed extensively[25,44]). The use of ANT DBS has been additionally reported in Dravet syndrome,[45] refractory status epilepticus,[46] and in patients with epilepsy refractory to VNS therapy.[47] The first notable modern case series was an open-label study of 5 patients with refractory epilepsy implanted in bilateral ANT in which Hodaie et al[48] showed a 54% seizure frequency reduction with a 15-month average follow-up and Kerrigan et al[49] found 4/5 patients with a clinically significant seizure frequency reduction, especially of secondarily generalized and seizures with impaired awareness. However, it should be noted that reductions in seizure frequency were not significant when pooled across all patients in this series, indicating the intersubject variability. Lee et al[50] published a larger series of 15 patients and reported a 70% reduction in seizure frequency with a 27-month average follow-up. Oh et al[51] showed improved neuropsychological scores in verbal fluency and verbal memory in 9 ANT DBS patients after 1 year of therapy and an average seizure reduction of 57.9%. A single-center retrospective study of 29 consecutive patients over 11 years showed 62% to 80% seizure frequency reduction with a 70-month median follow-up. In contrast to SANTE, this group did not note a trend to progressive efficacy with the reduction in either the seizure frequency or the responder rate with continuous use.[52] The variability in seizure frequency reduction among patients may be an innate characteristic of the underlying network such as functional connectivity between the ANT and the default mode network[53] and remains under investigation. ANT-DBS has been considered in a recent Delphi consensus statement.[54] They note that although many technical facets of ANT-DBS remain under investigation, such as the timing of turning on the stimulator and trajectory, the efficacy of ANT-DBS has been consistently shown.[54] Favorable outcomes with a lower side effect profile have been localized to the anterior–superior portion of the anterior nucleus,[55,56] targeting the junction of the ANT-MTT border,[57] and proximity to the wall of the lateral ventricle.[58]

Targeting

Appropriate targeting methods are of importance in considering ANT-DBS. Targeting has evolved from coordinate-based systems to the use of electrophysiology vs poor-quality imaging techniques and most recently direct targeting with higher field MRI and improved image quality. Direct targeting includes the use of specific MRI sequences such as Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR).[59] Direct targeting was shown to be superior to microelectrode recording of ANT,[60,61] specifically when targeting the anteroventral thalamus.[62] Although neurophysiological measures such as driving response have been shown to have limited utility in deriving correct placement,[63,64] different spiking patterns have been found in different areas of ANT,[65] suggesting a potential future utility. Hand-in-hand with targeting methods, a variety of trajectories have been shown to be efficacious for ANT, including the most common transventricular trajectory [66] and less common transcortical, posterior,[67] and parietal extraventricular trajectories.[68] An observational database study showed that a transventricular trajectory was more likely to provide accurate electrode placement within the ANT target, with 90% of electrodes having at least 1 electrode in ANT, as compared with 79% in extraventricular trajectories.[66]

Adverse Events

There have been some reports of worsened mood disorders, depression, and memory impairments with ANT-DBS; however, the long-term follow-up of the SANTE trial did not find a significant association between ANT-DBS and worsened mood disorders.[69] There are some case series data that have suggested neuropsychological and cognitive effects with chronic ANT stimulation, including decreased response inhibition,[70] sleep disruption,[71] and psychiatric adverse effects[72] perhaps related to ANT interaction with the vigilance networks.[73]

CONCLUSIONS AND FUTURE DIRECTIONS

DBS is a safe and effective neuromodulatory strategy to reduce seizure frequency in medically refractory causes of epilepsies. Patient selection and surgical and stimulation strategies are best performed by a multidisciplinary team of experts, including neurosurgeons and epileptologists, with patient input. RCT evidence suggests that, in appropriate and carefully selected patients with focal-onset epilepsy, with or without secondary generalization, DBS can modulate seizure networks to result in a progressive reduction in seizure frequency. Future and ongoing investigations include stimulation of other brain areas,[74] improvement in peri-ictal consciousness,[75,76] and DBS in pediatric populations suffering epilepsies.[77,78]

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Disclosures

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