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

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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 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 (ASSFN) 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 1/3 of epilepsy patients suffer with medication-refractory epilepsy.
• A persistent underuse of epilepsy surgery exists.
• Neuromodulation treatments including DBS expand the surgical options for epilepsy patients 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 two (or more) appropriate and adequately-dosed anti-seizure medications;
• Either partial-onset seizures with a localized onset in a region not amenable to resection or following failed resective surgery or focal-onset seizures with 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, as TMS therapy is contraindicated for patients with 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 are unacceptable due to an underlying medical condition.

**Recommendations are based on:**
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 anterior nucleus of the thalamus (ANT) for the treatment of refractory focal-onset seizures.
Supporting literature

Background
Epilepsies are common, chronic, heterogeneous, and debilitating syndromes. The lifetime prevalence of epilepsy is 1% worldwide \(^1\). 30-40% of patients suffer medically-refractory epilepsy, as defined as resistant to two or more appropriate first-line and patient-tolerated anti-seizure medications \(^2,^3\). Epilepsies presenting with partial/focal-onset seizures, especially those associated with temporal lobe epilepsy, are over-represented amongst 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 done 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 altered level of consciousness (Engel I status) after 1 year in the surgical group compared to 8% with continued medical therapy. Long-term follow-up suggests that \(^7\) 50-60% of patients with temporal lobe epilepsy obtain Engel I status \(^9,^{10}\), whereas resective outcomes after extratemporal onset zones are less favorable at 40-50% \(^11-^{13}\). Recently, laser interstitial thermocoagulation therapy (LITT) 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, deep focal cortical dysplasias) \(^16,^{17}\).
For people suffering from medically-refractory epilepsy that are not candidates for resection or ablation, neuromodulation is an established treatment. Large randomized studies of vagus nerve stimulation (VNS) found 24.5-28% reduction in seizure frequency; long-term follow-up showed 44.1% of patients had >50% long term reduction in seizure frequency. Responsive neurostimulation (RNS), which is distinct due to its closed-loop ‘response’ to an electrographically-detected seizure, has been shown in the pivotal RCT to have 37.9% decrease in seizure frequency in a 12 week blinded period. Long-term follow-up showed 53% seizure reduction after a 2 year open label period, with long-lasting efficacy and even progressive median seizure reduction (75% reduction at 9 years). 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.

Anterior Nucleus of the Thalamus - DBS

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

The pivotal multi-center 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 two anti-epileptic drugs), partial-onset epilepsy. 60% of patients had temporal-onset seizures, 27.3% frontal-onset, and remainder of seizure-onsets included diffuse/multifocal/other (18.2%), parietal (4.5%) and occipital (4.5%). The main clinical endpoints were safety as defined by adverse events/SUDEP events, and efficacy as defined by seizure rate between active and control stimulations using generalized estimating equations. Secondary
endpoints 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 AEDs. 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 1). When patients were randomized in a 1:1 fashion, investigators observed a 17% decrease in total seizure rate in the blinded active (5V) vs control (0V) groups by post-hoc analysis (p=0.045), and a 38% decrease in median seizure frequency at 3 months of active stimulation compared to 14.5% with sham stimulation. Across the entire blinded phase, median seizure frequency was decreased by 35% with active stimulation and 21.1% with control stimulation (p=0.119). After 4 months following DBS implantation, all patients had active stimulation with programming restrictions and AED stability as an open-label unblinded phase (3-9 months after implant). There were no such restrictions in longer-term follow-up past 9 months after implant. Seizure frequency was progressively reduced with longer duration of use; median seizure frequency for years 1-7 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 after 5 years total 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 context of their low drop-out rate with 75 of 110 implanted subjects remaining active beyond 5 years 27.

A smaller RCT, designed in the same manner as SANTE, was 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 21% decrease in frequency of focal seizures with impaired awareness from baseline rates in active stimulation compared to baseline (p=0.038), but not significant compared 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=0.009)28. It was terminated early due to lack of 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 201829.

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, has 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 malfunction31. Rarely reported complications include wire-tethering strictures32, 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 shows a steady increase in the use of DBS as a neurostimulation strategy, and support its use for medically refractory epilepsy33-39. Prior systematic reviews have noted the lack of studies with direct
comparisons between neurostimulation strategies. Three rigorous systematic reviews of interest support the use of ANT DBS in medically-refractory epilepsy. Chambers and Bowen (2013) evaluated 11 studies regarding electrical stimulation for MRE, 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 since 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. Based on the SANTE RCT, they concluded ANT DBS was safe and well-tolerated, with high quality evidence suggesting 3 months of ANT DBS reduced seizure frequency, despite the potential reporting bias. They noted no significant impact on seizure freedom or responder rate. Boon et al included a systematic review of all available invasive and non-invasive neurostimulation techniques (including VNS, DBS, RNS, transcranial direct current stimulation (tDCS), transcutaneous VNS, transcranial magnetic stimulation (TMS), and trigeminal nerve stimulation (TNS)). For ANT DBS, they evaluated the SANTE RCT and the two prior systematic reviews; they summarized the prior 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.

Non-comparative studies

Numerous open-label studies and case series since the first human reports for ANT DBS in the 1980s show efficacy ranging from 24-90% seizure frequency reduction in generalized, focal, and secondarily generalized seizures (previously reviewed extensively). Use of ANT DBS has been additionally reported in Dravet syndrome, refractory status epilepticus, and in patients with epilepsy refractory to VNS therapy. The first notable modern case series were
an open label study of 5 refractory epilepsy patients implanted in bilateral ANT in which Hodaie et al (2002) showed 54% seizure frequency reduction with 15 month average follow-up\(^48\), and Kerrigan et al (2004) found 4/5 patients with 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 inter-subject variability \(^49\). Lee et al (2012) published a larger series of 15 patients and reported a 70% reduction in seizure frequency with a 27 month average follow-up\(^50\). Oh et al (2012) showed improved neuropsychological scores in verbal fluency and verbal memory in in 9 ANT DBS patients after 1 year of therapy and an average seizure reduction of 57.9% \(^51\). A single-center retrospective study of 29 consecutive patients over 11 years showed 62-80% seizure frequency reduction with 70 months median follow-up. In contrast to SANTE, this group did not note a trend to progressive efficacy either with reduction in seizure frequency or responder rate with continued use\(^52\). The variability in seizure frequency reduction amongst 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 while many technical facets of ANT-DBS remain under investigation, such as the timing of turning on the stimulator, trajectory, etc, the efficacy of ANT-DBS has been consistently shown \(^54\). Favorable outcomes with 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 is of importance in considering ANT-DBS. Targeting has evolved from coordinate-based systems, to 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 FGATIR. Direct targeting was shown to be superior to micro-electrode recording of ANT, specifically when targeting the anteroventral thalamus. While neurophysiological measures such as driving response has been shown to have limited utility in deriving correct placement, different spiking patterns have been found in different areas of ANT 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 trans-ventricular trajectory, and less common trans-cortical, posterior, and parietal extraventricular trajectories. An observational database study showed that a trans-ventricular 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 to 79% in extra-ventricular trajectories.

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. There are some case series data that have suggested neuropsychological and cognitive effects with chronic ANT stimulation, including decreased response inhibition, sleep disruption, and psychiatric adverse effects perhaps related to ANT interaction with the vigilance networks.

Conclusions and future directions
DBS is a safe and effective neuromodulatory strategy to reduce seizure frequency in medically-refractory causes of epilepsies. Patient selection, surgical and stimulation strategies are best performed by a multi-disciplinary 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 progressive reduction in seizure frequency. Future and ongoing investigations include stimulation of other brain areas\textsuperscript{74}, improvement in peri-ictal consciousness\textsuperscript{75,76}, and DBS in pediatric populations suffering epilepsies.\textsuperscript{77,78}.

**Figures**

**Figure 1**

![Figure 1](image)

Figure 1. Study design of the SANTE trial. Reproduced with permission\textsuperscript{26}.
References


