Deep brain stimulation for seizure control in drug-resistant epilepsy

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Antiepileptic drugs prevent morbidity and death in a large number of patients suffering from epilepsy. However, it is estimated that approximately 30% of epileptic patients will not have adequate seizure control with medication alone. Resection of epileptogenic cortex may be indicated in medically refractory cases with a discrete seizure focus in noneloquent cortex. For patients in whom resection is not an option, deep brain stimulation (DBS) may be an effective means of seizure control. Deep brain stimulation targets for treating seizures primarily include the thalamic nuclei, hippocampus, subthalamic nucleus, and cerebellum. A variety of stimulation parameters have been studied, and more recent advances in electrical stimulation to treat epilepsy include responsive neurostimulation. Data suggest that DBS is effective for treating drug-resistant epilepsy.

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KEYWORDS medically refractory epilepsy; catastrophic epilepsy; brain stimulation; seizures; epilepsy surgery; responsive neurostimulation

Epilepsy has an estimated lifetime prevalence of 7.6 cases per 1000 persons and an incidence of 68 cases per 100,000 individuals internationally.¹⁹ In the 2010 Global Burden of Disease Study, epilepsy was found to have a worldwide burden second only to migraine headaches among neurological disorders.²⁵ The International League Against Epilepsy defines drug-resistant epilepsy as a failure to achieve sustained seizure freedom after two appropriately chosen, tolerated, and scheduled antiepileptic drugs (AEDs), whether they are given as monotherapy or in combination.³³ Estimates of patients with drug-resistant epilepsy are as high as 30% but vary depending on the resistance criteria used and are generally slightly lower in more developed countries.³⁶

The mechanism by which the disorder is resistant to AEDs remains incompletely understood. The most prevalent explanations include the “target hypothesis” and the “transporter hypothesis.” In the target hypothesis, it is thought that changes in the AED targets, such as ion channels, lead to decreased drug efficacy. In contrast, in the transporter hypothesis, efflux pumps are thought to restrict AED movement into cells and to be overexpressed in patients resistant to AEDs.³⁶ P-glycoprotein (Pgp) is one such multidrug transporter that has been implicated in drug-resistant epilepsy. Significantly increased levels of Pgp have been found in patients with medically refractory epilepsy.³³ Among patients with drug-resistant epilepsy, adding surgical treatment is four times more likely to result in seizure freedom than medical treatment alone.³⁸ A meta-analysis of long-term (≥ 5 years) seizure freedom after epilepsy surgery revealed that 66% of patients who underwent temporal lobe resections were seizure free, though this figure was lower among patients requiring extratemporal resection.³² A review of nine systematic reviews and two large case series of patients with intractable epilepsy revealed a median 62.4% of patients to be seizure free after epilepsy surgery; however, surgery was found to be less effective for epilepsy not associated with structural pathology and/or extratemporal lesions.³¹ Better surgical outcomes were reported when seizures were associated with hippocampal

ABBREVIATIONS AED = antiepileptic drug; ANT = anterior nucleus of thalamus; CMT = centromedian nucleus of thalamus; DBS = deep brain stimulation; ECoG = electrocorticographic; RNS = responsive neurostimulation; SANTE = Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy; STN = subthalamic nucleus; TLE = temporal lobe epilepsy; VNS = vagus nerve stimulation.


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sclerosis and benign tumors. Mortality with epilepsy surgery was reported to be 0.1%–0.5%, and surgery is effective and safe for correctly selected patients.

In general, contraindications to epilepsy surgery include the lack of a discrete seizure focus, seizure foci involving eloquent cortex, or significant comorbidities such that the patient is not medically stable for resective surgery. For patients whose epilepsy is refractory to medical therapy and who are not good candidates for resective epilepsy surgery, other treatment options are available. Nonsurgical therapies that may reduce seizures in appropriately selected patients include the administration of a ketogenic diet and, to a lesser degree, the use of cannabidiol, although current data are conflicting as to their efficacies.\textsuperscript{17,49,72} Vagus nerve stimulation is less invasive than resective surgery and improves seizure control in carefully selected individuals.\textsuperscript{16,25,47} Deep brain stimulation (DBS) is another promising treatment modality that has shown efficacy in decreasing seizure frequency in patients with refractory epilepsy.

**Mechanism of Action and Preclinical Data**

Deep brain stimulation’s mechanism of action in treating epilepsy remains poorly understood. Stimulation may, in fact, disrupt pathological network activity by reducing neuronal activity in the stimulated target.\textsuperscript{43} However, studies have shown complex patterns of excitation as well as inhibition with DBS.\textsuperscript{50} Animal studies have demonstrated that high-frequency stimulation of the anterior nucleus of the thalamus (ANT) leads to cortical desynchronization and may be protective against seizures, whereas low-frequency stimulation provokes seizures.\textsuperscript{48} Rhythmic stimulation from DBS has been likened to a pacemaker that helps to synchronize thalamocortical networks and prevent the disorganized cortical spread thought to underlie seizures.\textsuperscript{33} The optimal stimulation parameters for any given DBS target are largely based on trial-and-error methodologies or the use of parameters that have been successful for other DBS targets. For example, some studies have demonstrated that the DBS current is more important than the stimulation frequency in pilocarpine-induced seizure models.\textsuperscript{24} However, the efficacy of hippocampal stimulation may be driven by the frequency of stimulation and may be independent of stimulation intensity.\textsuperscript{5}

Some literature suggest that at least part of the efficacy of DBS may simply be attributable to the lesional effect of electrode placement.\textsuperscript{5,6,14,28,38,64} However, this notion has been experimentally controlled for and debated by other groups.\textsuperscript{20,32,37,50,69} For example, a recent study examined nine patients with refractory epilepsy treated with DBS.\textsuperscript{13} These patients were followed up for changes in seizure rates after their stimulator battery had been depleted. Only two patients did not have changes in their seizure frequency, whereas seven (78%) had increased seizure frequency. Interestingly, five of the seven individuals still reported a seizure frequency less than even their baseline before DBS, suggesting that a portion of, but not all, seizure relief is due to the lesional effect. Many structures have been the target of stimulation in human trials to improve seizure control (Fig. 1 and Table 1), including the ANT,\textsuperscript{2,20,39,57} the centromedian nucleus of the thalamus (CMT),\textsuperscript{21,52,60,64} the cerebellum,\textsuperscript{4,65,69,75} the hippocampus,\textsuperscript{5,7,14,15,30,68,73} and the subthalamic nucleus (STN).\textsuperscript{10,26,36,71}

**Common DBS Targets**

**Studies on Targeting the ANT**

The ANT is divided into the anterodorsal, anteroven- tral, and anteromedial subnuclei, which all have distinct patterns of connectivity. These include widespread connections to the frontal lobes as well as to other members of the Papez circuit. The ANT receives inputs from the subiculum, the mammillary bodies via the mammillo-thalamic tract, and the retrosplenial cortex.\textsuperscript{29} This local network has further diffuse cerebral connectivity, which likely underlies its therapeutic potential for seizure control. Most available data suggest that ANT DBS is most useful for the treatment of partial and secondarily generalized seizures.

The highest quality data supporting the use of ANT DBS comes from the Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial. Results of this landmark multicenter, double-blind randomized study of bilateral ANT stimulation were reported in 2010.\textsuperscript{20} The study population consisted of patients ages 18–65 years with partial seizures, including secondarily generalized seizures, in whom at least three AEDs had failed. A criterion for study inclusion was seizures for at least 6 months,
but no more than 10 seizures per day. Patients with progressive neurological diseases were excluded, as were patients with nonepileptic seizures, those with an IQ < 70, or those who were pregnant. Patients who had undergone prior vagus nerve stimulation (VNS) device implantation and/or resection (53.6%) were allowed to enroll. A total of 110 patients underwent electrode implantation. After randomization, patients remained in the blind phase of the study for 3 months, then moved to a 9-month unblinded phase in which all patients received stimulation. During the blind phase, 36.3% of patients in the stimulation group experienced improvement in their complex partial seizures versus 12.1% of control patients who experienced improvement (p = 0.041). In addition, injuries occurring as a result of seizures were lower in the stimulation group (7%) than in the control group (26%; p = 0.01). Interestingly, patients previously implanted with a VNS device or who underwent resective surgery prior to DBS had outcomes that were not different from those in the patients who did not undergo these other procedures. Long-term results of the SANTE trial were published in 2015 and are even more compelling. At the 5-year follow-up, median seizure reduction from baseline was −69%, and participants had experienced a statistically significant increase in quality of life.

The results of many smaller unblinded trials have also been reported. In 2002, Hodaie et al. described the results of bilateral ANT DBS treatment in five patients with medically refractory epilepsy. They documented an average seizure reduction of 54% (range 24%–89%) at a mean follow-up of 15 months, with two patients experiencing a ≥ 75% reduction in seizures. Similarly, Andrade and colleagues obtained at least a 50% reduction in seizure frequency in five of six patients receiving ANT DBS. In a single-center prospective study, Kim et al. reported treating 29 patients with ANT DBS. They obtained a median seizure reduction of 71% at 1 year, 74% at 2 years, and 62%–80% from years 3 to 11.

### TABLE 1. Summary of studies using various targets for deep brain stimulation for intractable epilepsy

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No.</th>
<th>Target</th>
<th>Stimulation</th>
<th>Seizure Outcomes*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher et al., 2010; Sala-nova et al., 2015</td>
<td>110</td>
<td>Bilat ANT</td>
<td>5 V, 90 µsec, 145 Hz; 1 min on/5 mins off</td>
<td>69%</td>
</tr>
<tr>
<td>Hodaie et al., 2002</td>
<td>5</td>
<td>Bilat ANT</td>
<td>10 V, 90 µsec, 100 Hz; 1 min on/5 mins off</td>
<td>54% (24%–89%)</td>
</tr>
<tr>
<td>Andrade et al., 2006</td>
<td>6</td>
<td>Bilat ANT</td>
<td>1–10 V, 90–120 µsec, 100–185 Hz; continuous or 1 min on/4–5 mins off</td>
<td>≥50% in 5/6 patients</td>
</tr>
<tr>
<td>Kim et al., 2017*</td>
<td>29</td>
<td>Bilat ANT</td>
<td>1.5–3.1 V, 90 µsec, 130 Hz; continuous</td>
<td>62%–80% after 3–11 yrs</td>
</tr>
<tr>
<td>Velasco et al., 1995</td>
<td>5</td>
<td>Bilat CMT</td>
<td>0.45–0.8 A, 90 µsec, 65 Hz; 1 min on/4 mins off</td>
<td>Near abolition of GTC; no change in CPS</td>
</tr>
<tr>
<td>Fisher et al., 1992</td>
<td>7</td>
<td>Bilat CMT</td>
<td>Variable, 90 µsec, 65 Hz; 1 min on/4 mins off</td>
<td>30%</td>
</tr>
<tr>
<td>Valentin et al., 2013</td>
<td>11</td>
<td>Bilat CMT</td>
<td>≤5 V, 90 µsec, 60 or 130 Hz; continuous</td>
<td>6/6 w/ generalized epilepsy responded; 1/5 w/ focal epilepsy responded</td>
</tr>
<tr>
<td>Son et al., 2016</td>
<td>14</td>
<td>Bilat CMT</td>
<td>2.2 V, 120 µsec, 130 Hz; 3 mins on/2 mins off</td>
<td>68% (25%–100%), 11/14 responders</td>
</tr>
<tr>
<td>Velasco et al., 2006</td>
<td>13</td>
<td>Bilat CMT</td>
<td>0.4–0.6 A, 450 µsec, 130 Hz; 1 min on/4 mins off</td>
<td>80%</td>
</tr>
<tr>
<td>Boon et al., 2007</td>
<td>10</td>
<td>Bilat AH</td>
<td>2–3 V, 450 µsec, 130 Hz; continuous</td>
<td>710 responders</td>
</tr>
<tr>
<td>Boëx et al., 2011</td>
<td>8</td>
<td>Unilat AH</td>
<td>0.5–2 V, 450 µsec, 130 Hz; continuous</td>
<td>4/6 responders, 2 of whom were seizure free</td>
</tr>
<tr>
<td>Cukiert et al., 2014</td>
<td>9</td>
<td>Uni- or bilat HIP</td>
<td>1–3.5 V, 300 µsec, 130 Hz; continuous</td>
<td>76%–80% (unilat), 66%–100% (bilat)</td>
</tr>
<tr>
<td>Cukiert et al., 2017</td>
<td>16</td>
<td>Uni- or bilat HIP</td>
<td>2 V, 300 µsec, 130 Hz; continuous</td>
<td>50% achieved seizure freedom; 88% responders</td>
</tr>
<tr>
<td>Velasco et al., 2007</td>
<td>9</td>
<td>Bilat HIP</td>
<td>0.3 A, 300 µsec, 130 Hz; 1 min on/4 mins off</td>
<td>50%–70% (HS), &gt;95% (NLMTLE)</td>
</tr>
<tr>
<td>Tellez-Zenteno et al., 2006</td>
<td>4</td>
<td>Unilat HIP</td>
<td>1.4–7 V, 90 µsec, 190 Hz; continuous</td>
<td>15%</td>
</tr>
<tr>
<td>Chabardès et al., 2002</td>
<td>5</td>
<td>Uni- or bilat STN</td>
<td>1.5–5.2 V, 60–90 µsec, 130 Hz; continuous</td>
<td>64% in 4/5 patients</td>
</tr>
<tr>
<td>Lee et al., 2006</td>
<td>3</td>
<td>Bilat STN</td>
<td>0.8–3.2 V, 60 µsec, 130 Hz; continuous</td>
<td>49%</td>
</tr>
<tr>
<td>Handforth et al., 2006</td>
<td>2</td>
<td>Bilat STN</td>
<td>≤3.5 V, 60–90 µsec, 130–185 Hz; continuous</td>
<td>50% &amp; 33%</td>
</tr>
<tr>
<td>Vesper et al., 2007</td>
<td>1</td>
<td>Bilat STN</td>
<td>2.5–3 V, 90 µsec, 130 Hz; continuous</td>
<td>50%</td>
</tr>
<tr>
<td>Van Buren et al., 1978</td>
<td>5</td>
<td>Bilat CH</td>
<td>10–14 V, 10–200 Hz; continuous</td>
<td>No objective benefit</td>
</tr>
<tr>
<td>Bidzinski et al., 1981</td>
<td>14</td>
<td>Bilat CH</td>
<td>1–7 V, 10 Hz; continuous</td>
<td>Seizure freedom in 5/14; no benefit in 3/14</td>
</tr>
<tr>
<td>Velasco et al., 2005</td>
<td>5</td>
<td>Bilat CH</td>
<td>2.28 V, 450 µsec, 10 Hz; 4 mins on/4 mins off</td>
<td>59% (25%–86%)</td>
</tr>
<tr>
<td>Wright et al., 1984</td>
<td>12</td>
<td>Bilat CH</td>
<td>7 mA, 10 Hz; intermittent &amp; continuous</td>
<td>No benefit</td>
</tr>
<tr>
<td>Gwinn &amp; Morrell, 2017</td>
<td>175</td>
<td>Depth or subdural electrodes</td>
<td>Commonly 1.5–3.0 mA, 160 µsec, 100–200 Hz; responsive stimulation</td>
<td>73%</td>
</tr>
</tbody>
</table>

AH = amygdalohippocampus; CH = cerebellar hemisphere; CPS = complex partial seizure; GTC = generalized tonic-clonic seizure; HIP = hippocampus; HS = hippocampal sclerosis; NLMTLE = nonlesional mesial temporal lobe epilepsy.

* Except where noted, percentages indicate the mean or median percent reduction in seizure frequency from baseline. Ranges are noted in parentheses. Patients designated as “responders” indicate ≥50% reduction in seizure frequency.
Studies on Targeting the CMT

The CMT, together with the parafascicular nuclei, form the posterior group of the intralaminar nuclei of the thalamus. The motor cortex provides input to the CMT, as do the globus pallidus interna (GPI). The CMT projects back to the motor cortex as well as the striatum with particular preference for the putamen and the head of the caudate nucleus proximal to the internal capsule. The majority of available data support the use of CMT DBS for the treatment of generalized epilepsy, including patients suffering from Lennox-Gastaut syndrome.

After publishing their preliminary results in 1987, Velasco et al. provided long-term follow-up data on bilateral CMT DBS in 1995. Five patients followed up between 7 and 33 months experienced near abolition of generalized tonic-clonic seizures. Interestingly, however, there was no reported change in the number of complex generalized tonic-clonic seizures. Two of the remaining patients with intractable epilepsy using bilateral CMT DBS. They reported a 30% decrease in generalized tonic-clonic seizures with stimulation in the on mode versus 8% when the stimulator was off. In addition, three of six patients who entered the follow-up segment of the study experienced at least a 50% reduction in seizure frequency. Likewise, a two-center single-blind trial of CMT DBS in 11 patients reported that only one of five patients with frontal lobe epilepsy had > 50% improvement in seizure frequency, whereas all six patients with generalized epilepsy had such improvement. The authors concluded, as many other groups have, that CMT DBS may be more effective for patients experiencing generalized epilepsy. In a study of 14 patients with refractory epilepsy, Son et al. reported a mean seizure reduction of 68% (range 25%–100%) at an average follow-up of 18.2 months. In total, 11/14 patients attained a > 50% reduction in their seizure frequency. Other patients with generalized seizures, such as those with Lennox-Gastaut syndrome, may have an improved response to CMT DBS. In another study by Velasco et al., 13 patients with Lennox-Gastaut were treated with bilateral CMT DBS. Overall seizure reduction was reportedly an astonishing 80%.

Studies on Targeting the Hippocampus

The hippocampus is an essential component of the mesial temporal lobe and the Papez circuit. It is formed from the dentate gyrus and the pyramidal layer, further divided into four zones labeled as cornu ammonis (CA) 1–4. The perirhinal and parahippocampal cortices supply the entorhinal cortex, which also receives input from the amygdala, piriform cortex, insula, basal forebrain, frontal cortex, thalamus, brainstem, and basal ganglia. The entorhinal cortex in turn projects to the hippocampus. The Papez circuit continues by projections from the subiculum to the fornix, the mamillary bodies and mammillothalamic tract, the ANT, the cingulum, and back through the entorhinal cortex. There is further spread to the cerebral cortex through many of these structures. Deep brain stimulation to the hippocampus or other mesial temporal lobe structures has been focused on the treatment of mesial temporal lobe epilepsy (TLE).

Anterior temporal lobectomy or selective mesial temporal resection can lead to seizure freedom in 70% of patients. Approximately 30% of patients with TLE are unsuitable for resection due to bilateral disease or concern for verbal memory loss after amygdalohippocampectomy, such as those with nonlesional left TLE. A report published in 2007 detailed a pilot study of 10 consecutive patients with refractory mesial TLE treated with amygdala-hippocampal DBS. Two patients were followed up for an average of 31 months, and seven of the 10 patients experienced a seizure reduction of at least 50%. A separate trial treated eight patients with drug-resistant epilepsy using amygdala-hippocampal DBS. The two patients with hippocampal sclerosis experienced a 65%–75% decrease in seizure frequency. Two of the remaining patients with nonlesional mesial TLE became seizure free.

In a 2014 study, Cukiert et al. treated nine patients with refractory TLE using hippocampal DBS. Patients with unilateral hippocampal sclerosis were treated with unilateral DBS and had a 76%–80% reduction in seizure frequency. Patients with bilateral hippocampal sclerosis (n = 4) received bilateral implants. Three of these patients received unilateral stimulation and experienced a 66%–100% reduction in seizure frequency. Patients without lesonal mesial TLE received bilateral implants and were treated with unilateral stimulation (n = 2, 80% and 97% reduction in seizure frequency) or bilateral stimulation (nonresponder). The authors subsequently reported the results of their prospective, randomized double-blind study. The trial enrolled 16 patients with refractory TLE who underwent implantation of hippocampal leads and were randomized to stimulation on or off arms. While a lesonal effect was noted, 50% of the treatment group experienced complete seizure freedom and 88% were considered responders. Velasco et al., for a period ranging from 18 months to 7 years, followed up nine patients who had undergone hippocampal DBS. The four patients with hippocampal sclerosis experienced a 50%–70% seizure reduction, whereas the five patients with nonlesional mesial TLE experienced > 95% seizure reduction. Not all studies have yielded such robust results. Tellez-Zenteno et al. reported on four patients with drug-resistant mesial TLE treated with left hippocampal DBS; median seizure reductions were a meager 15%.

Studies on Targeting the STN

The STN is a highly vascular nucleus located between the zona incerta and the cerebral peduncle. Itsafferent fibers chiefly include those from the cerebral cortex and the globus pallidus externa (GPe), as well as the centromedian/parafascicular nuclei. It projects mainly to the globus pallidus and substantia nigra reticulata (SNr), though it also has connections with the striatum, substantia innominata, and cerebral cortex, among others. Its utility in the treatment of epilepsy is still unclear, and additional trials are needed to determine which patients can most benefit from this target.

By far, the most well-studied indication for DBS in the STN is for movement disorders such as Parkinson’s disease. It has also been studied for the treatment of neuro-psychiatric disorders such as severe obsessive-compulsive disorders.
Several studies have examined the potential utility in the treatment of drug-resistant epilepsy. Chabardès et al. reported a mean seizure reduction of 64.2% experienced by four of five patients, whereas no effect was noted in the fifth. In another small cohort of three patients, Lee et al. noted mean seizure reductions of 49.1% after STN DBS. Additional small uncontrolled studies exist, though large randomized trials are needed to determine the efficacy of STN DBS for its utility in refractory epilepsy.

Studies on Targeting the Cerebellum

The cerebellum is situated caudal to the cerebrum. It is connected to the rest of the CNS by the three paired cerebellar peduncles. Cerebellar afferents arrive by way of the inferior (from inferior olivary complex, pons, dorsal spinocerebellar tract, and vestibular system), middle (corticopontine fibers), and superior cerebellar peduncles (ventral spinocerebellar tract). Efferents, mainly from the deep nuclei, leave via the inferior and superior cerebellar peduncles. The cerebellum is well described for its participation in motor control. However, emerging research also suggests that the cerebellum plays an important role in cognition and has been found to participate in cerebral association networks. While the cerebellum has the longest history in DBS for the treatment of epilepsy, results have been mixed. Therefore, stimulation of the cerebellum has fallen out of favor.

A study published in 1978 detailed the treatment of five drug-resistant epilepsy patients with bilateral cerebellar hemisphere stimulation. No observable decrease in seizure frequency was reported. In another study published in 1981, 14 epilepsy patients were treated with bilateral cerebellar hemisphere stimulation. The authors reported seizure elimination in five cases and a failure to significantly change seizure frequency in only three cases. A double-blind randomized pilot study treated five drug-resistant epilepsy patients with bilateral cerebellar hemisphere stimulation. Patients initially randomized to the stimulator-off mode did not experience a reduction in seizures, whereas patients randomized to the stimulator-on mode had 33% seizure reduction. After a 6-month follow-up in which all patients received stimulation, the authors reported a mean seizure reduction of 41% compared to baseline. In a separate study of 12 patients with intractable epilepsy treated with cerebellar stimulation, no reduction in seizure frequency was reported at 6 months.

Responsive Neurostimulation

Responsive neurostimulation (RNS) is a unique implantable electrical current delivery method that does not rely on continuous or predefined intermittent stimulation paradigms. The treating physician programs the RNS device to recognize electrocorticographic (ECoG) patterns unique to the patient that may occur prior to ictal onset. When the patient subsequently experiences similar ECoG activity, the device delivers a high-frequency stimulation impulse to either the cortical surface via subdural grids or the deep structures via depth electrodes (Fig. 2). This benefits the patient in several ways. Most obviously, it serves as immediate treatment for impending seizures rather than relying on timing as with an on/off stimulation paradigm. Because the system only fires when it detects aberrant ECoG activity, battery life is prolonged. Developed by NeuroPace, the RNS system was approved by the FDA in 2013 for the treatment of refractory partial seizures in adults. This was based on data obtained from the pivotal 2011 trial that demonstrated patients with drug-resistant epilepsy receiving RNS had, on average, 37.9% fewer seizures, compared to the sham group’s decreased seizure rate of 17.3%. Importantly, quality of life also improved in these patients. Inclusion criteria were patient ages 18–70 years and three or more simple partial, complex partial, or secondarily generalized seizures each month despite a minimum of two AEDs. Patients were excluded if they experienced nonepileptic seizures, had primarily generalized seizures, had progressive CNS or another significant medical disorder, or had undergone a recent neurosurgical or VNS implant procedure. Long-term data are also available for RNS and are even more striking. A median seizure reduction of 53% was observed at 2 years in 230 patients. Importantly, 44% of participants have also reported meaningful improvement in quality of life at 2 years. At 8 years, median seizure reduction has been reported to be 73% (175 patients).

Complications of DBS

When considering complications associated with DBS used to treat epilepsy, it is important to examine safety results obtained from the highest quality studies, including the SANTÉ trial. Long-term safety results from the SANTÉ trial showed that the most common adverse event associated with DBS was implantation site pain (23.6%). Paresthesias were also common, occurring in 22.7% of patients. Implant site infection occurred in 12.7% of patients, and lead misplacement occurred in 8.2%. Less common
adverse events included dizziness (6.3%), lead fracture (5.5%), and lead migration (5.5%). Overall, serious adverse events occurred in 33.6% of patients over 5 years, which includes 10% experiencing implant site infection and 8.2% with leads in an incorrect location.57 While the RNS NeuroPace system can utilize depth electrodes similar to those of traditional DBS devices, it differs significantly because the generator is implanted inside the cranial vault. This presents a number of potential disadvantages, including the need for access to the skull whenever the system must be replaced. In addition, any infection would take place closer to the brain and CSF spaces.

It is important to consider the possibility of exacerbating seizures or inducing new seizures when offering DBS as a treatment for epilepsy. A review of 2101 electrode placements across 16 reports revealed an incidence of new-onset seizures in up to 13% of patients.12 At least 74% of seizures occurred around the time of electrode placement, with many patients experiencing intracranial hemorrhage. In this analysis, the authors estimated that DBS is associated with a < 2.4% (95% CI 1.7%–3.3%) risk of seizures and that the postprocedural risk of seizures from chronic DBS was approximately 0.5% (95% CI 0.02%–1.0%).12 A separate report examined 161 patients who had 288 leads placed.54 Among these patients, 4.3% experienced seizures. The vast majority (86%) of seizures occurred within 48 hours after lead implantation.

Deep brain stimulation appears to be a relatively safe procedure, with most complications appearing during or around the time of electrode implantation. This is not to say, however, that implantation techniques cannot be improved upon. As an example, in 2015 Van Gompel et al. released a report that described a novel trajectory to the ANT that may be safer and may provide a method of assessing the Papez circuit to provide electrophysiological confirmation of lead placement intraoperatively.66 Emerging technologies such as near-infrared spectroscopy and intraoperative MRI may increase the accuracy of probe placement and decrease complications.9,22

Summary

Deep brain stimulation is a safe and efficacious treatment for drug-resistant epilepsy. It is effective in reducing seizure frequency in patients who otherwise have no other treatment options. Some patients treated with DBS can attain seizure freedom. The targets chosen for DBS vary and mainly include the ANT, the CMT, and the hippocampus. Specifically, patients with partial seizures or secondarily generalized seizures may benefit more from ANT DBS, whereas those with generalized epilepsy such as in Lennox-Gastaut syndrome may benefit more from CMT DBS. Individuals with mesial TLE may benefit from hippocampal DBS. As hardware and implantation techniques continue to improve, the safety of these procedures will also improve. Perhaps most importantly, additional large randomized double-blind trials will help to solidify the efficacy of DBS and increase its utilization.

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Author Contributions
Conception and design: Mittal. Acquisition of data: Klinger. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: Mittal. Reviewed the final version of the manuscript on behalf of both authors: Mittal. Administrative/technical/material support: Mittal. Study supervision: Mittal.

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