Judgment is not ignorance

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Crossroads: Two Points of View

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YES, NEUROSTIMULATION HAS A ROLE IN THE MANAGEMENT OF EPILEPSY

The treatment of epilepsy involves 4 modalities: medications, neurostimulation, diet, and surgery. The proportion of medically refractory patients remains around 30%, despite new medications, justifying the need for nondrug treatments. In fact, the use of nondrug treatments is one of the key roles of a comprehensive epilepsy center.

Resective surgery is potentially curative, and should remain the first choice at level IV centers. Advances in neuroimaging and other technologies allow for better localization for resective surgery, even for nonlesional extratemporal focal epilepsy. Among comprehensive centers, there is substantial variability in the use of neurostimulation vs surgery.

Until recently, the only Food and Drug Administration (FDA)–approved device in the United States was vagus nerve stimulation (VNS), which has been evaluated by the American Academy of Neurology and American Epilepsy Society.[1–3] Real-world experience, whereas not as rigorous as the initial controlled study,[4] has supported its efficacy.[5,6]

The field of neurostimulation for epilepsy is evolving. Recently, the FDA approved a responsive cortical neurostimulator (RNS)[7]; deep brain (anterior thalamic nucleus) stimulation (DBS)[8] has been approved in several countries and may be in the United States. Other modalities are under investigation and available outside the United States (e.g., external neurostimulation in Europe). All neurostimulation treatments are palliative (negligible seizure-freedom rates), and they are not designed to replace potentially curative resective surgery. The consensus, therefore, is that neurostimulation should be preceded by a thorough surgical evaluation (though possibly not in some children).

Neurostimulation devices appear comparable to each other in efficacy, with responder rates of 23%–30% in short-term double-blind trial periods, and 35%–43% (open label) at 1 year.[9] Choice, then, is based on other factors such as safety, tolerability, and possible positive effects on comorbidities and quality of life. There would be little justification for using RNS or DBS prior to VNS, with the probable exception of RNS for long-term recording purposes—the RNS records seizure activity in addition to treating. Similarly, if a less invasive (transcutaneous) device were FDA-approved, it would logically be tried prior to VNS.

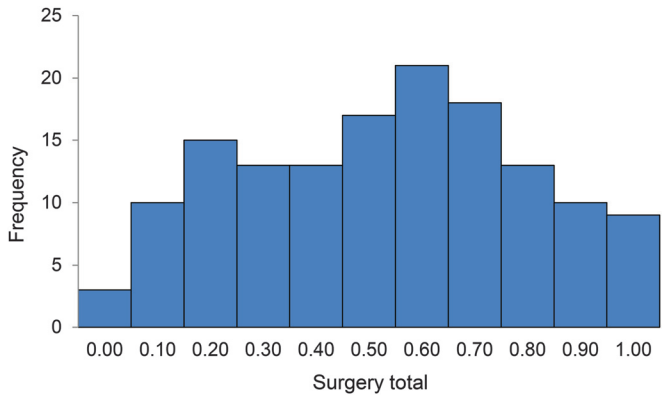
Decisions about resective surgery or stimulation may vary depending on a number of factors. Outcome of surface video-EEG and neuroimaging determines "resective surgery candidacy," with best-to-worst likely outcomes ranked in the following order: (1) unilateral mesiotemporal; (2) lesional neocortical; (3) bilateral mesiotemporal; (4) nonlesional neocortical with side or lobe known; and (5) nonlesional neocortical with side and lobe unknown.[10] Other conditions with likely poor outcomes for resective surgery include symptomatic or primary generalized epilepsies. There is no consensus of which patients to investigate with invasive EEG, so approaches vary among epilepsy centers. These challenging cases are typically debated at multidisciplinary epilepsy management conferences.

All comprehensive epilepsy centers encounter patients with refractory epilepsy for whom surgery is not an option, and at least 20% of resective surgeries do not result in seizure freedom. Shouldn't neurostimulation be considered in these patients?

Data from the National Association of Epilepsy Centers for 2012, on 142 level IV epilepsy centers, reveal a total of 2,281 surgeries and 2,439 neurostimulation procedures. Variability was measured using the proportion [surgery/(surgery + neurostimulation)]. This variable had a near-normal distribution (figure), with a mean of 0.49 and SD of 0.263.

Using a 90% "normal" range of 6%–92%, 10% would be outliers, which represented 12 centers in our sample: 5 had a proportion <6% (too few surgeries), 5 had a proportion >92% (too few neurostimulation implantations). Using an 80% "normal" range of 16%–82%, 20% would be outliers, representing 38 centers: 20 with proportion <16% (too few surgeries) and 18 with proportion >82% (too few neurostimulation implantations). For neurostimulation use, then, 5 centers are outliers defined by 90% and 18 are outliers defined by 80%, compared to their peers. Two centers had zero neurostimulation implantations, vs 25 and 30 surgeries, and 3 centers had zero surgeries, vs 8, 13, and 20 neurostimulation implantations, which we find equally unhealthy.

Figure Distribution of the proportion: Surgeries/(surgeries + neurostimulation)



Based on National Association of Epilepsy Centers data from 2012 on 142 level IV centers.

Why would a level IV center not use a treatment option (neurostimulation) that is standard of care? Some common arguments against VNS, for example, do not convince:

1. "There are many patients for whom VNS has not worked." Perhaps true, but palliation plays an important role for such patients. VNS may have fewer adverse effects than an additional medication.
2. "The level of evidence is low." Low level of evidence is better than no evidence; VNS has (modest) evidence for (modest) efficacy. The pivotal E03 and E05 VNS studies could not be fully blinded because the stimulation can be felt. However, DBS and RNS were not perceivable, so the benefit of stimulation here was not due to placebo effect. The literature now includes 4 (2 VNS, 1 DBS, 1 RNS) large, randomized, placebo-controlled trials documenting efficacy.[1–4,7,8]
3. "Once implanted, patients cannot have MRIs." This is a valid point for RNS (contraindicated), VNS (brain MRI possible with send-receive coil), and DBS.
4. "We offer it but patients decline." This is largely dependent on the style of the presentation. Any treatment (e.g., vigabatrin, felbamate, surgery) can be presented in a positive or a negative way.

Efficacy and tolerability of neurostimulation are well-documented. No large, randomized trial has failed to show efficacy. The effect is modest but has proven replicable. Further, the arguments against stimulation are weak. There should be a place for neurostimulation at all level IV centers. In many situations, the choice is often between neurostimulation and trying yet another antiepileptic drug. Some centers appear to prefer the latter.

Skepticism is healthy. Ignoring data and available treatment modalities is not.

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JUDGMENT IS NOT IGNORANCE

We disagree with the statement that "There would be little justification for using RNS or DBS prior to VNS."[1] In fact, the efficacy of both deep brain stimulation (DBS) and responsive neurostimulation (RNS) was superior to that of vagus nerve stimulation (VNS) in the respective pivotal clinical trials, an important result given that trials of the DBS and RNS were properly blinded and had strict entry criteria requiring proof that enrolled participants had epileptic seizures. Additionally, patient subgroups with bilateral independent temporal onsets did better than participants as a whole in both the RNS and DBS trials, suggesting that cranially implanted devices may be preferred to VNS in specific clinical situations.

Whereas some patients are not surgical candidates, and others have suboptimal results after surgery, the important question is not whether neurostimuluation can be considered in these patients but rather when stimulation can be considered: before or after surgery. Put differently, when is an invasive or resective procedure expected to have only a palliative effect worthwhile? In our experience, the answer to this question varies according to the circumstances, but a clear discussion about the expected outcome and its practical consequences is the most critical factor for patients to make an informed decision.

We take issue with the methodology of identifying centers as outliers based on their rate of use of stimulation. The premise is that being an outlier is equivalent to being wrong, and the implication is that these supposed "wrong" practices are based on ignorance or bias. Until we have better data about the specific indications for each of the available devices, physician judgment in the context of each patient's complex clinical circumstances should be accorded appropriate respect.

Benbadis is correct that "Skepticism is healthy. Ignoring data and available treatment modalities is not." But exercising judgment, based on limited data and experience, is our job.

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NEUROSTIMULATION FOR THE TREATMENT OF EPILEPSY: THE SKEPTICAL VIEW

Great debates erupted in the late 19th century over the therapeutic value of electrotherapy to the brain before interest eventually waned.[1] We now have 3 electrical stimulation devices for the treatment of epilepsy (2 approved in the United States, a third in Europe). What do they offer and when should we consider their use?

Vagus nerve stimulation (VNS) was approved in the United States in 1997. In 2 double-blind randomized controlled trials,[2] mean seizure reduction ranged from 24.5% to 28%, with 50% responder rates of 31% and 23%, comparable to that of a newer drug.[3,4]

Open-label uncontrolled observations of the original cohorts showed 7% higher 50% responder rates at 1–5 years.[5] In a 2011 meta-analysis of 2,634 VNS patients, 4.6% became seizure-free.[6] Whereas VNS has a good safety record, all the authors have encountered patients with serious adverse events, including implant infection and respiratory complication, that required implant removal or device deactivation. The device limits MRI studies that can be critical when reinvestigating for possible epilepsy surgery. Head transmit and receive coils are required and sequences such as those for functional imaging cannot be performed. Finally, we have encountered patients implanted with VNS without preoperative video-EEG who later turned out to have nonepileptic seizures as the sole explanation of their attacks. The most appropriate use of VNS may be in the palliation of multifocal epilepsy, and as an alternative to corpus callosotomy in patients with refractory generalized epilepsy.[5]

Anterior thalamus stimulation (ATS) was approved in Europe in 2010 based on a double-blind, randomized, sham stimulation–controlled trial involving 110 patients.[7] The Food and Drug Administration (FDA) has so far refused approval in the United States on examination of the same trial data. Median seizure reduction was 40% in the active treatment arm, with further reduction to 56% in unblinded extension at 25 months. Eight patients (7.3%) were seizure-free for at least 1 year, and 4 (3.6%) for at least 2 years. The trial recognized an acute lesion or implantation effect with reduction in seizure frequency of 22% seen during the month prior to initiation of stimulation. Bilateral implantations are required, and asymptomatic hemorrhages were detected by neuroimaging in 4.5% of procedures. Communication with individual European centers performing ATS suggests that neuropsychiatric decompensation, particularly depression, may occur. Patients with intractable generalized epilepsy were not studied, but based on current understanding of its pathophysiology, could potentially benefit.

Responsive neural stimulation (RNS) received FDA approval in November 2013 based on a randomized, double-blind, sham stimulation–controlled trial in 191 patients,[8] and has engendered excitement as "the" new therapy for epilepsy. During the 12-week blinded treatment period, mean seizure reduction was 37.9% in the active stimulation vs 17.3% in the sham control group, but the 50% responder rate was identical at 29% and 27%, respectively. In common with other neurostimulation studies, the 50% responder rate increased in the unblinded phase, reaching 43% at 1 year and 55% at 2 years.[9] Two participants (2.1%) were seizure-free during the blinded treatment period and 16 (9%) were seizure-free in the last 3 months of unblinded follow-up at 2 years. Intracranial hemorrhage occurred in 4.7% and device or wound infection in 5.2% of subjects. It is unclear if precise localization of the epileptogenic zone to guide electrode placement affects efficacy, as only 59% of subjects had prior intracranial EEG. How much benefit of the device derives from responsive stimulation to abort seizures as originally conceived? The median number of stimulations delivered by a typical RNS device is 500 times daily, or 20 times an hour, close to the fixed-rate neuromodulatory paradigm of VNS and ATS, although the total stimulation time is much less. RNS may also turn out to be a useful, if expensive, intracranial long-term monitoring system for epilepsy. Patients often have many more seizures than they themselves recognize, and long-term intracranial EEG detection offers new insights into seizure dynamics. RNS may be most appropriate in patients with seizures arising in unresectable eloquent cortex, and in patients with bitemporal or bifocal epilepsy, as it can differentiate between unifocal or bifocal epileptogenicity with the potential to select one for definitive surgical resection.

VNS has become widely adopted and is now estimated to account for 50% of surgical procedures for epilepsy in the United States and United Kingdom. At the same time, the number of resections for epilepsy in the United States has plateaued or is declining.[10] At present, neurostimulation mainly provides palliation, whereas complete or near-complete seizure control is a prerequisite for normal health and socialization in patients with epilepsy. For comparison, in the only randomized controlled trial of surgery for temporal lobe epilepsy,[11] the seizure-free rate at 1 year was 58% after surgery vs 8% in those treated medically. For this reason, neurostimulation devices including VNS should not be implanted before a thorough evaluation to assess surgical candidacy and exclude nonepileptic events, and ought to be reserved for those who are not candidates for surgical resection, or unwilling to consider surgery. Stimulation as a substitute for medication has been largely disappointing in our hands. New diagnostic and surgical approaches are continuously adding to the pool of surgical candidates from patients previously thought to be nonsurgical. A half-hearted presurgical workup is a great disservice to these patients, and centers with limited technological resources may need collaborative help from others to fully assess surgical candidacy. Once an intracranial device is implanted, the use of many MRI-based diagnostic innovations may be difficult to impossible. Patients and physicians also need more data on long-term efficacy and adverse effects of a permanently implanted device; thus a rigorous system to capture key outcomes of device-based treatment would be of great value.

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SKEPTICISM SHOULD NOT RESULT IN IGNORING A TREATMENT OPTION

We agree with some of the arguments of So et al.[1] to justify the skepticism of "refractory" epilepsy centers.

- "It limits MRI." We agree.
- "We see patients with vagus nerve stimulation (VNS) without prior EEG-video." We agree this should almost never be done. (A possible exception, mostly in children, is in the setting of typical Lennox-Gastaut syndrome with daily major motor seizures that can be captured on a brief EEG.) Here, *prolonged* EEG-video could conceivably be omitted. However, the *wrong* use of VNS (without prior EEG-video) is not an argument against its *correct* use.
- "VNS is for palliation of multifocal epilepsy." We agree, but this is not the only indication. It also has a place after failed resective surgery,[2] and for the occasional "primary" (idiopathic, genetic) generalized epilepsy that is truly intractable.[3] Some centers, including pediatric, do not use it even for the obvious indication of "palliation of multifocal epilepsy" even where there are no other options than endless combinations of antiepileptic drugs (AEDs).
- Adverse events. Serious adverse events with VNS are rare and generally benign. If the concern is safety, then responsive cortical neurostimulator (RNS) should not be preferred over VNS, but it sometimes is, especially (not coincidentally) at centers that were RNS trial sites. No doubt RNS is more elegant and "sexier," but it does not appear safer or more effective. In addition, AED polypharmacy also has adverse events.
- Neurostimulation is not competing with resective surgery; it is a palliative complement for it. It makes no sense for centers to perform many surgeries but no neurostimulation, yet some centers do just that. Similarly, it makes little sense to jump onto RNS but not use VNS, yet some centers do just that.
- Skepticism is healthy and would be justified if it resulted in some (albeit unenthusiastic) use of neurostimulation and VNS. The part we object to is when skepticism results in neglecting an available treatment even where there are no other options.

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