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CURRENT PERSPECTIVES

Comparison and Selection of Current Implantable Anti-Epileptic Devices

Stephen Wong[1] · Ram Mani[1] · Shabbar Danish[2]

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Abstract
Implantable neural stimulators represent an advanced treatment adjunct to medication for pharmacoresistant epilepsy and alternative for patients that are not good candidates for resective surgery. Three treatment modalities are currently FDA-approved: vagus nerve stimulation, responsive neurostimulation, and deep brain stimulation. These devices were originally trialed in very similar patient populations with focal epilepsy, but head-to-head comparison trials have not been performed. As such, device selection may be challenging due to large overlaps in clinical indications and efficacy. Here we will review the data reported in the original pivotal clinical trials as well as long-term experience with these technologies. We will highlight differences in their features and mechanisms of action which may help optimize device selection on a case-by-case basis.

Key Words Neurostimulation · vagus nerve stimulation · VNS · responsive neurostimulation · RNS · deep brain stimulation · DBS · epilepsy · seizures

Introduction

Approximately a third of epileptic individuals will continue to experience seizures despite successive trials of anti-convulsant medications [1]. Among these individuals, only a minority will be candidates for surgical resection. For the remainder of individuals, electrical neurostimulation and neuromodulation is a palliative option that has seen increasing utilization over the past two decades.

The modern era of human brain stimulation in epilepsy began with Sir Victor Horsley in 1886 when he utilized electrical cortical stimulation for mapping to aid in brain resection in a patient with focal epilepsy [2]. Cortical stimulation to define brain function was significantly expanded by the work of Penfield and Jasper in their landmark monograph published in 1954 [3]. These studies ushered in a golden age of cortical mapping and animal neuroscience studies.

Electrical stimulation was first used therapeutically for epilepsy in the 1970s, when the cerebellum became the first therapeutic target for electrical stimulation in human patient epilepsy, with mixed results [4–6]. These initial efforts paved the way towards deep brain stimulation (DBS) in a number of subcortical targets for various neurological disorders. In addition to the cerebellum, the main targets for DBS in epilepsy have been the thalamus (discussed in greater detail below), hippocampus [7–12], and subthalamic nucleus [13–16].

Peripheral nerve stimulation has also proven fruitful for stimulation in epilepsy. Vagus nerve stimulation (VNS) in humans was initially published in 1990 [17], long after earlier stimulation studies performed by Bailey in 1938 in cats reported cortical EEG changes [18]. Observations of cessation of grand mal seizures by applying pressure on the intraorbital trigeminal nerve were first reported in 1976 [19]. Based on common afferent targets of the trigeminal nerve and vagus nerve, the external trigeminal neurostimulator (eTNS) was developed as a non-invasive alternative to VNS [20, 21]. This technology received the European CE Mark in 2012; the device is still investigational in the USA.

The treatment of epilepsy through neocortical stimulation began when Lesser reported that pulse stimulation could

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✉ Stephen Wong
stephen.wong@rutgers.edu

[1] Department of Neurology, Rutgers – Robert Wood Johnson Medical School, 125 Paterson St., Ste 6200, New Brunswick, NJ 08901, USA

[2] Department of Neurosurgery, Rutgers – Robert Wood Johnson Medical School, New Brunswick, NJ, USA

terminate afterdischarges induced during cortical stimulation in 1999 [22]. This idea was explored further with closed-loop abortion of seizures in small cohorts of patients undergoing intracranial epilepsy monitoring with subdural grids [23, 24] and eventual multi-site clinical trials (discussed below). Recently, chronic subthreshold cortical stimulation (CSCS) to prevent neuronal recruitment into the epileptic focus prior to macroscopic seizure detection has been applied with promising results in small series [25, 26].

Steady effort and investigation after this early work in peripheral nerve, neocortical, and subcortical stimulation have culminated in FDA approval for VNS (LivaNova, London, UK) in 1997, responsive neurostimulation (RNS, NeuroPace, Mountainview, CA) in 2013, and DBS of the anterior nucleus of the thalamus (ANT-DBS, Medtronic, Minneapolis, MN) in 2018. These three technologies represent the state-of-the-art neurostimulation options that are currently available in the USA for patients with pharmacoresistant epilepsy who are otherwise poor surgical candidates. Physicians have continued to gain experience with the technology and the devices have continued to evolve after their initial efficacy was established in pivotal clinical trials. In this review, we will examine the three FDA-approved devices and review their features, mechanisms of action, and efficacy data. With these considerations, we will offer recommendations on device selection for particular patient populations.

Device Overviews

VNS

Overview

In this technology, stimulating electrodes are coiled around the left vagus nerve and tunneled subcutaneously to connect to an implantable pulse generator (IPG) placed in the left subclavicular region. This open-loop device delivers scheduled electrical stimulation to the vagus nerve, typically every several minutes for 30–60 s. The output current is typically titrated up to at least 1.50 mA over at least 10–12 weeks after implant based on tolerability. The patient is also provided a wrist magnet to swipe the pulse generator and deliver an extra "dose" of stimulation. In 2015, the AspireSR® model was introduced which incorporated tachycardia-based seizure detection to deliver automated stimulation. In 2017, the newest Sentiva™ model was introduced, which includes the ability for differing stimulation during day *vs* night and tracking prone position and bradycardia (features that are risk factors for SUDEP [27]). As of 2018, more than 100,000 patients have had the VNS implanted, and it is utilized in several countries worldwide [28].

Mechanism of Action

The mechanism of action (MOA) by which VNS exerts its anti-seizure effect was previously considered unclear. But work throughout the years has shed significant light on the underlying mechanisms. Vagal afferents, which comprise 80% of the nerve, synapse mainly onto the nucleus of the solitary tract (NTS). The solitary nucleus' subsequent projections to the locus coeruleus (LC) and dorsal raphe are thought to mediate therapeutic effects of VNS in epilepsy and depression.

VNS' main anti-seizure effect is thought due to its influence on the LC and subsequent increase in CNS noradrenergic tone. LC has widespread projections to forebrain, limbic system, and spinal cord. In addition to a general arousing effect, there is a wide body of literature suggesting that NE in the CNS is anti-epileptic [29–33]. Evidence includes attenuation of the VNS anti-seizure effect in animal models of seizure after both chronic lesioning and acute inactivation of LC [34].

Vagal efferents, which comprise 20% of the bulk of the nerve, are thought to mediate the majority of the stimulation-related side effects of VNS for epilepsy. Laryngeal motor dysfunction and paresthesia are common and generally well-tolerated and are due to stimulation of CN X fibers originating from nucleus ambiguus (NA) innervating skeletal laryngeal musculature. Bradycardia or heart block can be caused by stimulation of CN X fibers originating from the NA that innervate parasympathetic cholinergic neurons (the atrioventricular and sinoatrial nodes are predominantly innervated by the left and right CN X, respectively); the incidence of this after VNS implantation is low, however, and only at the level of case reports [35–37]. GI side effects and anorexia arise from stimulation of CN X efferents that originate from the dorsal nucleus of the vagus nerve and synapse onto autonomic ganglia in the viscera.

Efficacy and Tolerability

VNS efficacy was most clearly established with two randomized, double-blind, controlled clinical trials known as the E03 (multinational sites) and E05 (US sites only) trials [38–42]. Patients 13 years and older with medically refractory focal epilepsy participated. Study designs (Fig. 1) between these two trials were identical and featured a 12- to 16-week pre-implant evaluation period to establish baseline seizure frequencies, followed by implantation and randomization 2 weeks postoperatively to receive "high" (active, titrated to tolerance) and "low" (control, titrated to the threshold of patient perception) stimulation. Two weeks after this, seizure reduction was measured for a 12-week blinded evaluation phase (BEP).

The primary endpoint of mean seizure reduction *vs* controls throughout the BEP was met in both trials and was 18.4%

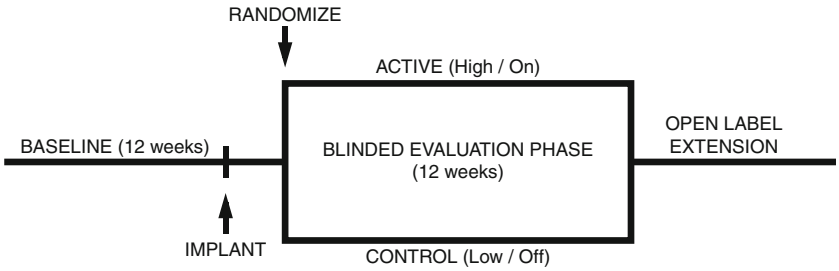

Fig. 1 VNS, RNS, and DBS common pivotal trial design. The pivotal trials for VNS, RNS, and DBS featured the common trial design below. The time from implant to randomization (the postoperative recovery period) was typically 4 weeks, but the RNS trial featured an additional 4 weeks for parameter optimization prior to the blinded evaluation phase. RNS and DBS active *vs* control arms were stimulation on *vs* off, *vs* VNS trials' active and control arms were stimulation high *vs* low.

(24.5% active *vs* 6.1% control) for E03, and 12.7% (27.9% active *vs* 15.2% control) for E05. A secondary endpoint 50% responder rate was statistically significant in E03 at (31% active *vs* 13% control), but not E05 (23.4% active *vs* 15.7% control). Since these studies, VNS use has markedly expanded for patients' age, with children as young as 3 years old receiving effective and safe therapy from it.

Long-term uncontrolled studies of patients with focal, multifocal, and generalized epilepsy with a variety of seizure types (e.g., tonic-clonic, focal seizures with impaired awareness, absence, and drop attacks) and epilepsy syndromes have demonstrated safety and efficacy of VNS. VNS long-term data were reviewed in an evidence-based guideline in 2013 [43] which highlighted two class III trials. One trial featured median seizure reductions and responder rates of 40% and 43%, respectively, at 3 years [44], and the other 63.8% and 64.4% at 5 years [45]. The largest long-term cohort of VNS had median seizure reduction of 56% with mean follow-up of 4.9 years for the 436 pediatric and adult patients. The median weekly seizure frequency reduced from 4 to 1.5 [46]. A recent large cohort of children and adults in Japan implanted with VNS featured median seizure reduction and 50% responder rates of 66.2% and 58.8% at 3 years [47]. Significant improvement in quality of life (QoL) was also seen in patients undergoing VNS implantation *vs* best medical therapy alone in a more recent multicenter randomized clinical trial in adults with pharmacoresistant focal epilepsy [48]. One large database study demonstrated that SUDEP risk decreased significantly (i.e., from 2.47 to 1.68 per 1000 patient-years) in the 10 years after VNS initiation [49]. It should be noted that the study was funded by the manufacturer and included co-authors that were employees or consultants for the manufacturer.

One potential benefit of VNS is its improvement of treatment-resistant depression (TRD) independent of seizure benefit. Active or recent depression prevalence is estimated in 13–37% of patients with epilepsy, and the number is higher in uncontrolled epilepsy [50]. The FDA approved VNS in 2007 for TRD, although Medicare and other insurers have not commonly reimbursed VNS for TRD due to their arguments that it is unproven [51]. As of 2018, six clinical trials for VNS in TRD exist and all studies show anti-depressant efficacy with response rates ranging from 30 to 53% [51], while established treatments NOT using VNS demonstrate 1-year responses rates of approximately 10% [52]. From an FDA-mandated registry, Aaronson showed at 5-year follow-up that VNS plus treatment as usual compared to another group with treatment as usual had higher cumulative response rates (68% *vs* 41%) and remission rates (43% *vs* 26%) in a cohort of 795 patients with TRD [53].

VNS side effects most commonly occur during electrical pulse delivery. Hoarseness, coughing, and laryngeal paresthesia are commonly reported (20–60%) and tend to improve with parameter reduction and over the long-term [28]. Less commonly, dyspnea or laryngismus (3–15%) occur with stimulation and improve with adjustment and time [41, 42]. Surgical site infection is relatively low and is greater in children than in adults (4% *vs* 1%) [43]. We expect that rate can be further reduced by fastidious bandage coverage of implantation site in children to avoid picking. Another probable side effect of VNS, though with limited investigation, is worsening of sleep-disordered breathing. A few small series have reported newly diagnosed or worse obstructive sleep apnea (OSA) in patients after VNS therapy initiation. In two studies of 18 and 23 patients, 22–58% had newly diagnosed OSA and 50% had worsening of preexisting OSA [54, 55]. It can be improved with device adjustment and/or continuous positive airway pressure therapy.

RNS

Overview

The RNS is a "closed-loop" device with sensing capabilities to deliver temporally targeted therapy upon detection of an epileptic seizure. It can currently detect and stimulate seizures originating from up to two seizure foci. The IPG is implanted with a craniotomy to allow it to sit continuous with the skull under the scalp. Lead implantation often requires prior intracranial EEG to localize seizure foci for optimal seizure detection and stimulation. Initially rated at 3–4 years' battery life,

the most recent IPG is advertised to remain operational to 8.4 years under "medium" stimulation settings. Patients are given a magnet to swipe the device to record electrocorticograms (ECoG) for physician review; the magnet can also act as a failsafe to temporarily stop stimulation, should the patient think they are experiencing adverse events due to stimulation. They are also given a laptop and telemetry wand to send recorded ECoG clips (including automated detections, scheduled, and magnet-triggered) and stimulation data to a secure Internet database that in turn can be accessed by physicians and company clinical engineers to optimize device parameters. Updated parameters are uploaded to the patient's device during clinic visits. A notable feature of this technology is that it enables a form of chronic ambulatory EEG monitoring. Patients generally do not detect stimulations at therapeutic settings.

Mechanism of Action

The main MOA by which RNS exerts its anti-seizure effect is broadly via acute electrical disruption of synchronous activity at its origin that is necessary for continuation/propagation of ictal activity. Early *in vitro* work on hippocampal slices exhibiting epileptiform activity due to penicillin, elevated extracellular potassium, or lower extracellular calcium demonstrated the anti-epileptic effect of pulsed anodal low-amplitude stimulation [56–58]. The mechanism was determined to be due to suppression of intracellular activity due to membrane hyperpolarization caused by a portion of the extracellular currents that cross into the cell, rather than desynchronization or synaptic effects. Another potential mechanism is axonal conduction blockade via high-frequency stimulation [59, 60]. In addition to acute abortive effects, long-term effects are posited to be due to gene expression changes and subsequent synaptic plasticity, cortical reorganization, or neurogenesis induced by chronic stimulation [61–63].

Efficacy and Tolerability

RNS efficacy was established in a placebo-controlled randomized clinical trial carried out in US sites with results published in 2011 [64]. Study design is summarized in Fig. 1. After a 12-week baseline period, patients were implanted with the device. Four weeks after implantation, patients were randomized to active *vs* control (stimulation OFF) arms, with an additional 4 weeks of stimulation optimization prior to a 12-week BEP. After the BEP, all subjects' stimulators were turned on for open-label evaluation.

Mean seizure reduction *vs* controls throughout the BEP was 20.6% (37.9% active *vs* 17.3% control). Because of a transient implantation effect, however, mean seizure reduction compared to controls improved over the course of the BEP, and the mean seizure reduction *vs* controls on a month-by-month basis was more robust at 32.1% during the final month of therapy. Median reduction *vs* controls throughout the BEP, reported in [65], was 8.8% (28% active *vs* 19.2% control). Fifty percent responder rates during the BEP was 29% and 27% in the treatment and control arms, a meager difference of 2% and not statistically significant.

Long-term effects of RNS were studied in an open-label long-term treatment trial, with results intermittently released for publication [66, 67]. Though largely mitigated by statistical adjustment, the usual caveats of potential survivorship bias due to possibly greater compliance or treatment benefit among those remaining in the study, as well as confounds from concomitant anti-epileptic drug (AED) therapy, may apply. The 1-, 2-, and 5-year median percent seizure reduction was 44%, 53%, and 48–66%, respectively. The manufacturer website advertises 73% median seizure reduction at year 8. Fifty percent responder rates at 1, 2, and 5 years were 44%, 55%, and 50–61%, respectively [66, 67]. QoL improved at 1 year postimplant and improvements were maintained through 5 years postimplant [67].

RNS appeared to be well tolerated, with adverse events only linked to the implantation procedure (hemorrhage in 4.7%, soft-tissue infection in 5.2% during the pivotal trial), without clear side effects attributable to stimulation. Most of the intracranial hemorrhages occurred in the days after implant, but three subjects in the pivotal trial had cerebral hemorrhages associated with strip or depth electrodes 2–3 years after the implant [67]. No differences in cognition or mood were observed during the pivotal trial or at 1- to 2-year follow-up [64].

DBS

Overview

DBS for epilepsy entails implantation of depth electrodes into the ANT to deliver scheduled stimulation. Depth electrodes emerge from the vertex and are tunneled subcutaneously to a pulse generator that is generally implanted in the subclavicular region. The advertised battery life for Medtronic's current lineup of Activa™ PC or SC IPGs ranges from 3 to 5 years, with reports indicating the shorter end of the range [68, 69], while their rechargeable RC model is replaced after 9 years.

Mechanism of Action

DBS is thought to functionally inactivate stimulated structures, though details are complex. Reports suggest high-frequency stimulation of subcortical structures can replace natural neural activity with spikes time-locked to the stimulation frequency [70, 71], possibly via excitation of axons and antidromic collision of natural spikes with stimulus-driven

spikes evoked at high frequency [72]; in this manner, propagation of ictal activity might be blocked.

DBS has its main use in Parkinson's disease and is a well-known, highly efficacious therapy that modulates dopaminergic basal ganglia circuits. A similar concept of neural circuit modulation is the basis for the anti-epileptic effect of DBS. The strategy of ANT-DBS in particular is to disrupt or modulate limbic circuits which may serve as conduit for propagation of focal seizures that impair awareness. As a primary relay nucleus in the circuit of Papez, the ANT contains afferent input from hippocampal subiculum via the fornix/mammillothalamic tract and has reciprocal connections to the frontal and cingulate cortex. Numerous pre-clinical studies have implicated the ANT and this circuit in the propagation of certain seizure activity [73–76].

ANT-DBS has the strongest data supporting its use in epilepsy, but other interesting results that support the concept of neural circuit modulation are from CMT-DBS [77–83]. The CMT has received input from motor and premotor cortex and basal ganglia and sends projections to the striatum. Perhaps unsurprisingly, CMT-DBS has been observed to abort generalized seizures, but not complex partial seizures, and has been proposed as a target for generalized epilepsy or Lennox-Gastaut syndrome [81, 84]. However, the CMT has not been targeted in larger trials for epilepsy after an early pilot study failed to demonstrate benefit [78].

Efficacy and Tolerability

Class I data from a double-blinded, randomized, controlled clinical trial of ANT-DBS was published in 2010 (a.k.a. SANTE trial, for Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy) [85]. Highly similar to the study design of the VNS and RNS trials (Fig. 1), subjects completed a 12-week baseline phase documenting seizure rates prior to implantation. After a 4-week recovery, patients were randomized to receive stimulation or not. Stimulation consisted of 1-min duration 90-μs pulses of 5.0V at 145 Hz, separated by 5 min. Seizure rates were observed for a 12-week BEP, followed by turning stimulation on for all subjects in a 9-month open-label phase.

Of note, one outlier subject in the DBS trial whose seizures dramatically worsened (210 seizures in 3 days compared to their baseline seizure rate of 19 seizures per month) necessitated outlier analysis to satisfy primary endpoints and played a role in delaying FDA approval for years, until long-term data demonstrated clearer benefit. With this outlier removed, median seizure reduction *vs* controls throughout the BEP was 13.9% (35.0% active *vs* 21.1% control). Similar to the RNS trial, there appeared to be an implantation effect with an initial seizure reduction in both groups early on that dissipated by the end of the BEP, resulting in median seizure reduction of 25.9% (40.4% active *vs* 14.5% control) during the final month. Fifty percent responder rates for active and controls were 29.6% and 25.9%, not statistically significant. A post hoc analysis of median seizure frequency reduction, stratified by lobe of onset, indicated statistically significant reduction for temporal lobe seizures during the BEP (43.9% active *vs* 29% control), but not for frontal or other lobes [85, 86]. In a similar vein, complex partial seizures were significantly reduced during the BEP compared to simple partial and partial to generalized seizures after outlier exclusion [86].

Long-term data [86, 87] indicate median seizure reduction at 1, 2, 5, and 7 years of 41.4, 55.6, 68.4, and 74.9%, with slight worsening using last-observation-carried forward analysis. Fifty percent responder rates at 1, 2, 5, and 7 years were 43.4, 53.7, 67.8, and 74%. Similar to the BEP, seizure reductions appeared best in the temporal lobe. Like the RNS long-term data, caveats include survival bias, and concomitant AED adjustment possibly accounting for a minority of the reported improvement. However, post hoc analyses comparing seizure frequency reduction by AED status (no change *vs* changes in AEDs) indicated parallel improvement in efficacy between the two groups, suggesting that stimulation efficacy in at least a portion of subjects continued to improve over time and was not driven by AED changes [86, 87]. QoL was improved 1 year after implant and remained significantly improved 5 years after implant [87].

Adverse events associated with ANT-DBS that occurred at any time over 5 years of long-term follow-up included implant site pain/paresthesias in approximately 20.9%, implant site infection in 12.7%, and lead mis-targeting in 8.2%. As for possible brain stimulation–related adverse effects, depression was reported in 32.7% (with one occurrence of suicide 4 years postimplant), and "non-serious" memory impairment in 25.5% [87]. It should be noted that 66% of the subjects reporting depression had a prior history. Additionally, specific neuropsychological measures for total mood disturbance and subjective cognitive function were not significantly different during the BEP between active and control when averaged over the entire study population [85], and actually improved statistically over the long term [87].

Device Comparison

Pivotal Trial Comparison

The trials above establishing efficacy for VNS, RNS, and DBS featured comparable patient populations (Table 1) and study designs (Fig. 1). Notable differences included only three seizures per month were required for RNS trial entry compared to six for the others; as such, the RNS population had the lowest seizure burden during the baseline phase, though this is probably not clinically significant. Another difference was since patients can perceive VNS, but not generally RNS or DBS, the

Table 1 Pivotal clinical trials—baseline characteristics [64, 65, 85, 86, 88]

	VNS (E03)	VNS (E05)	RNS	DBS
n	114	198	191	110
Epilepsy type	Focal	Focal	Focal	Focal
Years with epilepsy	21.8 ± 9.1	22.8 ± 11.1	19.6 ± 11.4	22.3 ± 13
Seizures per month: inclusion criteria	≥ 6	≥ 6	≥ 3	≥ 6 to ≤ 300
Seizures per month: observation period	45.0 (median 20.4 to 23.0)*	35.8 ± 61.5 (median 14.3 to 16.2)**	34.2 ± 61.9 (median 9.7)	56.1 ± 101 (median 19.5)
Prior surgery	31%	22.6%	32%	24.5%
No. of AEDs	2.0 ± 0.8	2.1 ± 0.7	2.9 ± 1.1	2.3 ± 0.7

*Calculated from [41] based on a 28-day month

**Calculated from [42] based on a 28-day month

E03 and E05 trials' control arms featured "low stimulation" parameters to maintain blinding at the cost of possible reduction of therapeutic signal, while the RNS and SANTE trials had stimulation turned entirely off for control patients. AEDs were held constant during the blinded phase of the trials.

Efficacy Comparison

Table 2 lists the total seizure reduction during the entire BEP of the device trials as well as the 50% responder rates. Mean seizure reduction throughout the BEP, compared to controls, was 18.4%, 12.7%, and 20.6% in the VNS E03 and E05, and RNS trials, respectively (note that the reduction based on a generalized estimating equations (GEE) model for RNS, compared to raw calculations in the VNS trials). SANTE utilized median statistics, with a 13.9% (35% *vs* 21.1%) median seizure reduction in active *vs* controls during the BEP. Both RNS and SANTE trials GEE models to estimate the number of seizures reduced in the treatment *vs* sham arms during the BEP. The RNS GEE model predicted a reduction of 5 seizures per month in a subject with 30 seizures per month at baseline. The DBS GEE model predicted a reduction of 3.6 seizures per month (21.1 control *vs* 17.5 active) with stimulation in a patient with a baseline of 26 seizures per month, after outlier exclusion. Aside from the E03 trial, none of the other trials demonstrated any difference in active *vs* control 50% responder rates during the BEP.

The long-term results for each of the devices, mentioned earlier, are plotted on Fig. 2 for a more direct visual comparison. All devices show improvement in efficacy over time, arguing for possible neuromodulatory effects that gradually change the epileptic network in addition to any acute seizure-abortive effects. Chronic stimulation may induce neural plasticity changes via positive (Hebbian) or negative (homeostatic synaptic plasticity) network regulatory mechanisms, operating on slower time scales, allowing portions of the network to effectively "unlearn" the epileptic state over many years. Overall, results were quite similar between DBS and RNS though DBS appears to continue to increase in efficacy many years out after RNS has plateaued. VNS results are variable depending upon the trial but are either comparable or slightly less efficacious than RNS or DBS over time.

Overall, efficacy appears to be similar between DBS and RNS, with a slight long-term performance edge for DBS. VNS performance trails somewhat, especially after considering implantation effects which may have diluted the BEP

Table 2 Pivotal clinical trials—blinded evaluation phase results. All numbers are means unless otherwise indicated. Seizure reduction in VNS trials were based on raw averages, whereas RNS and DBS were based on a GEE model. Note that these results are for the entire 3-month blinded evaluation phases, and to a degree under-estimates a cumulative effect of RNS and DBS as there was month over month separation of activation from control due to implantation effect (the final month of the 3-month BEP featured 41.5 active *vs* 9.4% control mean reduction in the RNS trial, and 40.4% active *vs* 14.5% control median reduction in the DBS trial). Results appear largely similar between devices

	n	% seizure reduction *vs* baseline		50% responder rate	
		Active	Control	Active	Control
VNS (E03)	114	24.5%	6.1%	31%	13%
VNS (E05)	198	27.9%	15.2%	23.4%^{NS}	15.7%^{NS}
RNS	191	37.9%	17.3%	29%^{NS}	27%^{NS}
DBS	110	35.0 (median)	21.1 (median)	29.6%^{NS}	25.9%^{NS}

^{NS} Not statistically significant

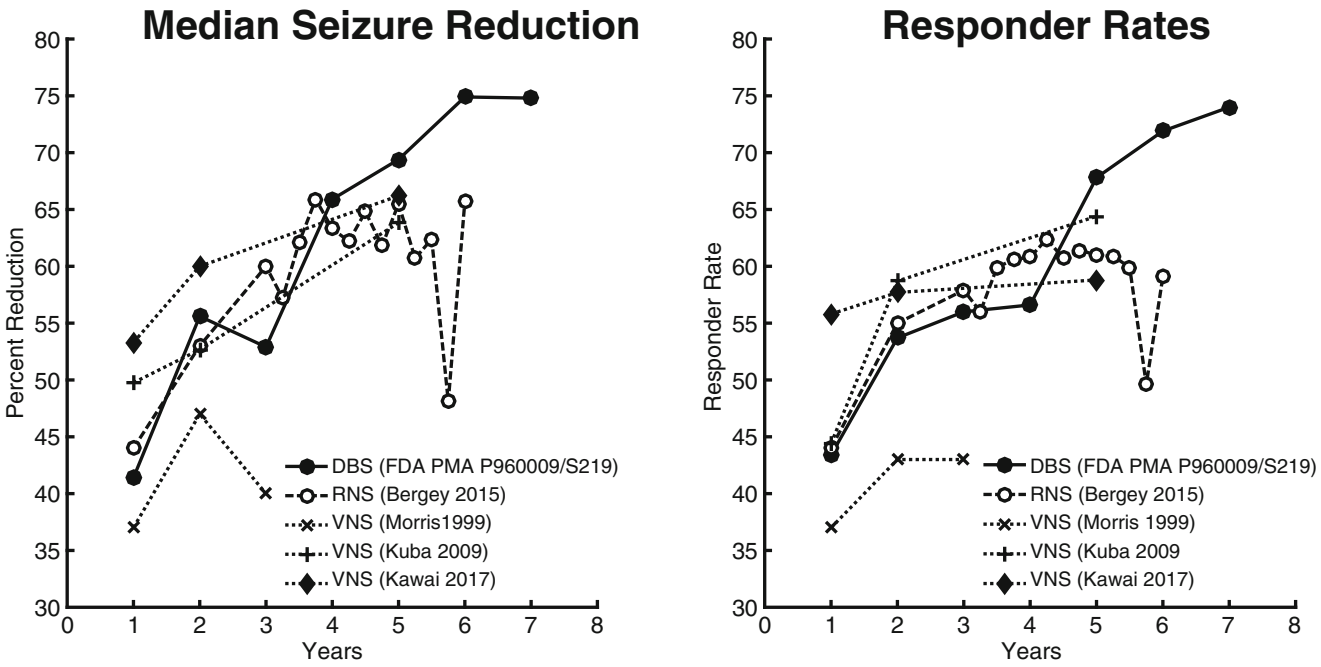

Fig. 2 Long-term VNS, RNS, and DBS median seizure reduction and responder rates. Unadjusted long-term seizure reduction and responder rates for VNS, RNS, and DBS [44, 45, 47, 67, 86]. Data from Kuba 2009 were calculated based on the baseline and 1-, 2-, and 5-year number of seizures per month provided in Table 1 of their manuscript, which indicate "mean" numbers, but the body of the manuscript and abstract imply that the Table 1 numbers were medians. DBS appears to have a slight long-term advantage, while VNS long-term results appear equal or slightly worse depending on the cohort. For a fair comparison, note that the numbers used from the original publications to form the graphs below were the unadjusted, declining numbers (and not the last observation carried forward numbers that were reported for some, but not all, studies).

numbers for RNS and DBS. Microlesional effects are postulated to disrupt the epileptic network at the site of electrode implantation and has been reported to be responsible for patients experiencing significant improvement in seizure control after intracranial EEG monitoring with either subdural electrodes or depth electrodes [89–91]. This effect would not have been expected to occur with VNS implantation.

There are several developments that may enhance the initially reported efficacy of the anti-epileptic devices. The literature suggests that 82% of patients experience abrupt tachycardia during seizures [92]. Controlled trials providing class I data of magnet stimulation in VNS do not exist, but a comprehensive review of VNS magnet use reported benefit in approximately 45%, for either seizure abortion or reduction with magnet swipe [93]. Limitations to magnet use during seizures include reduced patient awareness and function, unavailability of the magnet, and absence of a caregiver. Our own internal data from patients undergoing epilepsy monitoring suggest that only 13–15% of patients are able to press event buttons to notify nursing of their seizures [94]. If these figures can be extrapolated to VNS magnet use, the VNS autostimulation feature introduced in 2015 (provided with AspireSR® and SenTiva™ models) that deliver stimulation in response to tachycardia may produce added efficacy, in roughly up to 31% of patients compared to older models. Recent retrospective observations of patients experiencing further reduction in seizure burden after updating to an AspireSR® model during VNS battery change appear to support this [95].

Refinement of ANT-DBS surgical targeting and stimulation parameters that have only recently been reported. Increased efficacy may be associated with stimulation of the anterior portion of the ANT containing the anteromedial and the anterior principal subnuclei [96]. Furthermore, exploration of stimulation parameters may lead to increased efficacy with reduced psychiatric side effects [97]. These advances may lead to increased DBS efficacy compared to results reported in SANTE.

Feature Comparison

Table 3 lists specific feature comparisons between each VNS, RNS, and DBS. There are no significant feature drawbacks to VNS and it is the least invasive device compared to the others, but the efficacy may be more limited. RNS has several drawbacks, including (1) a frequent requirement for invasive intracranial EEG to localize onset prior to implantation of the device; (2) a cranial IPG implantation site, meaning battery changes are a scalp surgery; (3) inability of patients to get brain MRIs after implantation; and (4) requiring a motivated patient or caregiver (and usually a wired internet connection) for optimal device use. However, RNS has the longest advertised non-rechargeable battery life and is the only device

Table 3 VNS, RNS, and DBS features. Relative advantages are labeled in green, whereas relative disadvantages are labeled in red.

	VNS	RNS	DBS
Patient Population	Focal & generalized; pediatric and adult	1-2 foci; adult	Focal and generalized; adult
Lead Site	Neck	Variable; subdural strip / depth electrodes	Anterior Thalamic Nucleus
IPG Site	Subclavicular	Cranial	Subclavicular
Ease of Implantation	+++	+ (often requires IEEG)	++
Ease of Use	+++	+ (requires patient participation)	+++
Battery Life	++	+++	++
Side effects	+	+	++ (depression, memory)
Chronic Ambulatory EEG	Tachycardia Autostim Record only	ECoG / Stimulations	N/A
MRI-compatible	YES	NO	YES

capable of recording chronic ambulatory EEG, which may improve monitoring of seizure burden and possibly lead to palliative epilepsy surgery in bilateral patients whose epilepsy foci are found to produce vastly asymmetric seizure rates. Additionally, there do not appear to be significant neuropsychiatric side effects of therapy. The main advantages to DBS include its ease of use and slightly superior long-term efficacy, but this may be balanced by potential negative mood and memory effects associated with ANT stimulation. All three devices have relatively high theoretical benefit for patients with long-term AED compliance concerns. However, that same compliance concern may make optimal RNS usage difficult with data lost due to lack of uploads from the patient.

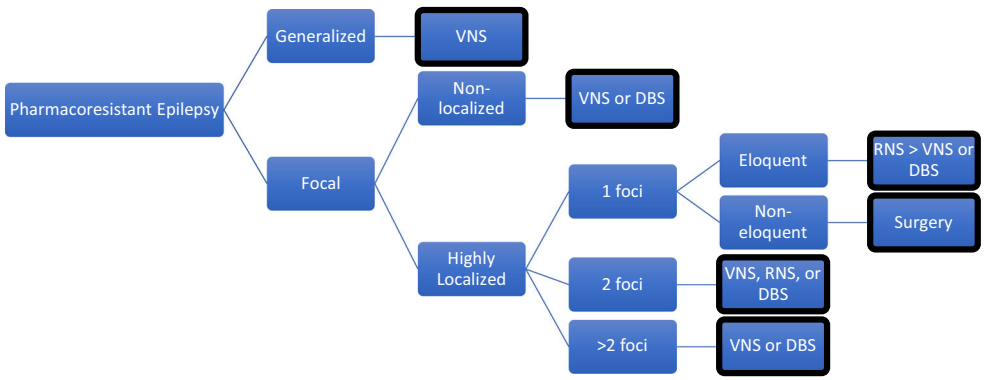

Fig. 3 Decision algorithm. The following shows a general algorithm for efficacious device selection based on mechanism of action and focality. If only considering efficacy, DBS may have an advantage if seizures are limbic/temporal compared to others at the same node. Other considerations (side effects, device features, and patient preferences) also drive device selection but are not captured in this flowchart.

Device Selection

As both short- and long-term efficacy appears not too dissimilar between devices, the main considerations for device selection may be MOA and individual device features. Patient preferences and comorbidities may heavily influence the latter considerations. Undergoing intracranial EEG to localize seizure foci prior to RNS implantation entails more morbidity compared to the other two devices. A lower level of motivation or adherence may be a red flag for optimal use of RNS, though the effort involved in data upload and parameter optimization generally becomes less intense over time. ANT-DBS should be used with care in patients at high risk for cognitive changes (e.g., the elderly) or in those with baseline mood disturbance. The latter group may receive benefit from mood-enhancing effects of VNS. VNS should be used in caution in those with, or suspected of having, sleep apnea.

In the absence of direct evidence, it may be a reasonable approach to match the device MOA and focality of treatment to the patient's epilepsy type and focality of disease. Each device can be differentiated based on the focality of their mechanism of action. The most diffuse is probably VNS, via its widespread influence on CNS noradrenergic projections. Indeed, multiple small open-label studies on VNS in Lennox-Gastaut syndrome and generalized epilepsy appear to demonstrate efficacy [98–101]. The most focal therapy is RNS, both spatially and temporally, interrupting the ictal onset zone during seizure initiation only. Temporal specificity, however, may not be entirely accurate as seizure stimulation due to noisy detection algorithms typically can lead to hundreds of stimulations per day (personal experience, [102]). If the majority of these are indeed false positive stimulations, RNS may possibly also be providing a degree of chronic stimulation of the ictal onset zone, similar to the approach that is being investigated with CSCS. Ideal patients include highly localized focal epilepsy patients with ≤ 2 foci, over eloquent cortex. In the middle ground is ANT-DBS, which disrupts limbic circuitry that may become involved in focal seizures with impairment of awareness. In support of this, patients with temporal lobe epilepsy and complex partial seizures exhibited statistically significant efficacy during the BEP of SANTE, possibly reflecting the role of mesial temporal structures in the circuit of Papez. Patients with strong limbic involvement of their seizures may be ideal candidates for ANT-DBS.

Figure 3 shows a decision flowchart mainly based upon focality of therapy. Note that other promising but investigational treatments such as CMT-DBS for generalized epilepsy, mentioned in the text above, are not considered. Considerations not captured in the flowchart include the specific location of the epileptic foci. For one focus in eloquent cortex, RNS may have an advantage over DBS and VNS, whereas ANT-DBS may be more efficacious in temporal lobe epilepsy and if limbic structures are involved (though the temporal lobe is likely non-eloquent). However, RNS appears to successfully treat bilateral hippocampal epilepsy without significant disruption in memory function [103]. In pure neocortical or frontal lobe epilepsy with up to two foci, RNS may be superior to ANT-DBS. For non-localized focal epilepsy or focal epilepsy greater than 2 foci, RNS would not be advised, and ANT-DBS may have greater efficacy over VNS.

Conclusions

The addition of new, well-tolerated brain stimulation options for the treatment of pharmacoresistant epilepsy represents a welcome crowding of the anti-epileptic device space. With more choice comes the responsibility to carefully consider each technology on a case-by-case basis for optimal treatment response. Head-to-head trials addressing efficacy and tolerability would be ideal for a more direct comparison between competing technologies. Further randomized controlled clinical trials are necessary to evaluate promising technologies such as eTNS, CMT-DBS, and CSCS, and may further broaden our treatment armamentarium.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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