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Therapeutic Devices for Epilepsy

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Abstract

Therapeutic devices provide new options for treating drug-resistant epilepsy. These devices act by a variety of mechanisms to modulate neuronal activity. Only vagus nerve stimulation, which continues to develop new technology, is approved for use in the United States. Deep brain stimulation (DBS) of anterior thalamus for partial epilepsy recently was approved in Europe and several other countries. Responsive neurostimulation, which delivers stimuli to one or two seizure foci in response to a detected seizure, recently completed a successful multicenter trial. Several other trials of brain stimulation are in planning or underway. Transcutaneous magnetic stimulation (TMS) may provide a noninvasive method to stimulate cortex. Controlled studies of TMS split on efficacy, and may depend on whether a seizure focus is near a possible region for stimulation. Seizure detection devices in the form of “shake” detectors via portable accelerometers can provide notification of an ongoing tonic-clonic seizure, or peace of mind in the absence of notification. Prediction of seizures from various aspects of EEG is in early stages. Prediction appears to be possible in a subpopulation of people with refractory seizures and a clinical trial of an implantable prediction device is underway. Cooling of neocortex or hippocampus reversibly can attenuate epileptiform EEG activity and seizures, but engineering problems remain in its implementation. Optogenetics is a new technique that can control excitability of specific populations of neurons with light. Inhibition of epileptiform activity has been demonstrated in hippocampal slices, but use in humans will require more work. In general, devices provide useful palliation for otherwise uncontrollable seizures, but with a different risk profile than with most drugs. Optimizing the place of devices in therapy for epilepsy will require further development and clinical experience.

Keywords

epilepsy; seizures; devices; brain stimulation; drug perfusion; vagus nerve stimulation; optogenetics; brain cooling; seizure prediction

Introduction

Devices do not cure epilepsy, but they may help to control otherwise refractory seizures. This overview will briefly summarize selected therapeutic devices being investigated as treatment for epilepsy. The review will not cover diagnostic devices related to EEG, MRI or PET scans, chemical delivery vehicles for drugs, gene therapy or radiation therapy, nor will it attempt to be comprehensive. With the exception of the vagus nerve stimulator, none of the devices discussed in this article are presently approved for use in the United States.

Seizure Alert System

Family members of a person with epilepsy may worry that a seizure is happening out of the range of observation, particularly while family members are asleep. Seizure monitoring devices are being developed to notify of an ongoing seizure. Seizure detection can be done by a variety of methods, including analysis of shaking produced by the patient or the bed¹, video algorithms detecting rhythmic movements², software to recognize electroencephalographic (EEG) patterns associated with seizures³, sounds made during a seizure⁴, and analysis of heart rate, rhythm or regularity⁵. Video-detection methods can recognize regular (rhythmic) movements across pixels of a digital image, but such recognition fails with patients under covers. Shake detectors only detect seizures with repetitive physical movements, but these are among the most worrisome and sudden death is more likely in people with uncontrolled tonic-clonic seizures⁶

Movement-based devices utilize accelerometers that can measure movement in real time, coupled with software. A “Multi-Modal Intelligent Seizure Acquisition System” developed in Denmark⁷ detected simulated seizures. Cuppens⁸ documented detection by accelerometers on the leg in three patients during the special case of frontal lobe seizures with pedaling movements. Sensitivity was 92% and specificity 84%. In two separate papers, Nijssen^{9,10} and colleagues reported accelerometer-based detection of tonic, myoclonic, tonic-clonic, and partial seizures with positive predictive value above 50%. Other authors^{2, 8} reported motion detection of seizures in neonates and in children with nocturnal frontal lobe seizures. One study of a Medpage® ST-2 bed shaking monitor¹ detected five of eight tonic-clonic seizures, but at a price of 269 false positive alarms.

Three portable devices recently have been developed to directly detect limb or body shaking by a patient having a tonic-clonic seizure. EpDetect (<http://www.epdetect.com/index.html>) uses accelerometers built into many smart phones to detect shaking in the 5 Hz frequency range, lasting for at least 10 seconds. After detection, the phone sounds an audible alarm, gives time to press a cancel button, and if not cancelled, automatically phones an alarm to up to three pre-determined caregivers. SmartWatch® comprises a wrist device with a miniature 3D accelerometer sensor programmed to detect rhythmic movements. A study of six patients with tonic-clonic seizures occurring in an epilepsy monitoring unit¹¹ detected 7 of 8 seizures, with one seizure missed because of battery depletion. One false detection occurred during sleep. Numerous false positive detections during waking could be canceled by the patient. A watch called EpiLert®¹², evaluated in 15 patients in an epilepsy monitoring unit, correctly identifying 20 of 22 seizures with 8 false alarms in 1,692 hours of monitoring.

Seizure Prediction

Having a seizure would not be nearly so troublesome if time of seizure occurrence were predictable¹³. A series of international workshops has reviewed goals and problems with seizure prediction¹⁴. Table 1 lists methods employed to predict seizures.

Patient Awareness

Temporal distribution of seizures is not random¹⁵. Some seizures cluster. Patients report precipitating factors or premonitory sensations for seizures¹⁶ that can serve as predictors of likely seizures. Haut and colleagues¹⁷ documented that 21% of 57 patients could predict seizures, with specificity of 90% and sensitivity of 37%. A study of 83 patients undergoing video-EEG monitoring¹⁸ observed a probability of having a seizure of 0.15 with negative predictions, versus 0.32 with positive predictions.

One of the earliest observations on seizure prediction was that of Wilder Penfield¹⁹, who observed blood flow changes in advance of clinical seizures. Weinand²⁰ noted a 20-minute preictal increase of blood flow in the temporal lobe giving rise to a seizure.

Prediction by EEG Features

An early attempt²¹ to use EEG pattern recognition to predict seizures was successful at detecting seizures, but impractical because of a high false-positive rate. Synchronization among different EEG channels tends to decrease just before a seizure²² and bursts of high-frequency activity appear.²³

Early seizure prediction models²⁴ utilized a new field called nonlinear dynamics or “chaos theory” to study the interictal-ictal transition. A standard EEG plot of voltage versus time does not display information about whether one time segment of the EEG is non-randomly related to another. Using nonlinear dynamics, Iasemides²⁵ asserted that “... the next seizure can be predicted 91.3% of the time, about 91 min prior to its onset, with the issue of 1 false warning every 8.27 h.” While this level of accuracy has not always been replicated, several other researchers have successfully employed nonlinear dynamic methods for seizure prediction.²⁶²⁷²⁸²⁹ One study³⁰ of 21 patients with implanted mesial temporal electrodes recording 88 seizures over 582 continuously recorded hours concluded that predictive ability was better than random, but sensitivity was only 21–42%.

Several EEG characteristics other than nonlinear dynamics have been used to attempt seizure prediction, including accumulated energy³¹, wavelets³² and baseline voltage crossings³³.

Seizure prediction and devices

A warning of an impending seizure has little value unless something is done to forestall the seizure or minimize its impact. At the simplest level, a warning of a seizure could enable a person to withdraw to a safer or less embarrassing environment for a seizure. The time horizon for the warning has to allow for such actions, but not so long as to produce ongoing anxiety.

A collaborative European effort called EPILEPSIAE (<http://www.epilepsiae.eu>, an acronym for “Evolving Platform for Improving Living Expectation of Patients Suffering from Ictal Events”) is collaborating with Micromed S.P.A.® (<http://www.micromed-it.com/>) to develop a database of ictal events in order to test prediction algorithms¹³. A second goal has been development of a portable EEG recorder using low power Bluetooth transmission technology. Clinical trials of seizure prediction using this device are in planning. In another effort, the National Institutes of Health has funded “The International Epilepsy Electrophysiology Database,” a platform based on cloud computing, to share large archives of expertly annotated human and animal intracranial EEG for collaborative research and benchmarking device performance. This database, promoted by the International Seizure Prediction Group, is working to share resources with EPILEPSAE.

NeuroVista® has developed a seizure advisory system, validated in canines with epilepsy³⁴ that has progressed to clinical trials in three hospitals in Australia (<http://clinicaltrials.gov/ct2/show/NCT01043406?term=neurovista&rank=1>). Recording strips of 16 electrodes are implanted subdurally, in and around the seizure onset region. These electrodes connect to a subclavicular unit that transmits EEG to a belt-worn device. The external device continuously analyzes intracranial EEG, and uses algorithms to determine the likelihood of seizure onset. The user is informed of seizure probability by a display of colored lights: blue for low likelihood, white for moderate likelihood or red for high likelihood and is provided with an audio alert when the seizure likelihood changes.

Once seizure prediction can be shown to have reasonable sensitivity and specificity, then the opportunity will be present for incorporation into “closed-loop” therapeutic devices. Such devices might stimulate brain or vagus nerve to reduce seizure likelihood, apply anti-seizure drugs to regions of brain or elsewhere, engage brain cooling devices, or instruct a patient to take a quick-acting (for example, nasal spray) medication dose.

Cooling

Cooling to temperatures below about 27° C can reversibly block synaptic transmission, and with it, epileptiform bursting in animal models.³⁵³⁶ Cooling therefore might provide a reversible means to inactivate a clinical seizure focus at a time of a seizure. In 1834, Jean Charles Peltier discovered that electrical current passed through two adjacent metal plates of different conductivity produces heat on one side and cold on another. Figure 1 shows a Peltier device placed on a seizure focus in an anesthetized rat (Fisher, unpublished). Epileptiform spikes recorded from bone screws in rat after placement of the GABA antagonist bicuculline methiodide 2 mM are displayed to the right of the figure (top two traces). Spikes decline with cooling cortex to 30° C (middle two traces), and return after rewarming to 37° C (bottom 2 traces). The effects of cooling with a Peltier device linked to software detection systems have been studied extensively by Rothman and associates³⁷.

In the clinical arena, cooling of brain has been attempted since the late 19th century. Systemic hypothermia was said useful in treatment of status epilepticus in six patients refractory to medications³⁸. Sourek and Travnicek³⁹ used air and ice cooling via skull burr holes in 23 patients with refractory epilepsy, Ommaya and Baldwin⁴⁰ interrupted status epilepticus in one patient and suppressed epileptic activity in six other patients by cooling brain with iced saline introduced by catheters placed bilaterally over cortex and into ventricles. One study of four patients with refractory status epilepticus showed benefit of endovascular cooling in terms of seizures, but one of the patients died of sepsis, possibly related to hypothermia⁴¹. A cooling microprobe to be inserted into tissue has been developed⁴². The major barriers to a practical cooling device are cooling sulci and deep brain tissue, dissipating heat, and obtaining an adequate portable power supply.

Optogenetics

Optogenetics, pioneered by Boyden and Deisseroth⁴³, employs optogenetics to control brain cell activity with visible light⁴⁴. Certain single-celled organisms that live in hostile environments utilize a protein similar to rhodopsin in our retina to regulate ion concentration in response to available light. These microbial opsin proteins act as ion channels or pumps so as to increase excitation or inhibition. Channelrhodopsin-2 (ChR2) produces immediate neuronal excitation in response to blue light; whereas, halorhodopsin (NpHR) produces inhibition in response to yellow-orange light. Rhodopsins are injected via viral vectors into a brain structure of interest. Transfection occurs in a subset of neurons and glia near the injection site. Additional molecular biological techniques can confer light sensitivity to specific subpopulations of cells. For example, after lentovirus delivery of the inhibitory halorhodopsin eNpHR3 to hippocampus, use of a calmodulin kinase promoter, CaMKII α , leads to relatively selective light sensitivity of pyramidal neurons and dendrites. The Cre-lox recombinant technique identifies specific stretches of DNA and splices it using Cre-recombinase. Lines of transgenic mice expressing Cre-recombinase in specific cell subtypes have been linked to rhodopsin genes, rendering only Cre-activated cell types light sensitive.

Reduction of neuronal firing by light-induced hyperpolarization should be adaptable to seizure control in suitable systems. Tønnesen and colleagues⁴⁵ injected a construct of lentivirus NpHR CaMKII α into hippocampus of rat pups. Hippocampal slices prepared subsequently showed pyramidal cell hyperpolarizations to orange light. Light also was able

to interrupt epileptiform stimulus-train-induced bursting. Figure 2 shows hyperpolarization and interruption of neuronal firing by orange light in hippocampal neurons transfected by halorhodopsin. In the lower traces epileptiform bursting induced by tetanic afferent stimulation is blocked reversibly by orange light.

The ability to selectively activate or inactivate certain specific neuronal populations likely will have game-changing impact on our understanding of functional neuroanatomy and neurophysiology in health and disease. Whether it will lead to a practical treatment for epilepsy is less clear. Barriers to applying optogenetic techniques for clinical epilepsy include the need for a conveniently implantable light stimulation system, demonstration of safety of viral transfection of these ion channels into human brain, and verification of long-term neural control, without producing unexpected changes in brain function.

Local Drug Perfusion

The 16th-century physician, Paracelsus, commented that the only difference between a drug and a poison is dose. With the possible exception of cancer chemotherapy agents, this observation is nowhere as true as with narrow-therapeutic-margin antiepileptic drugs. If we could deliver an antiepileptic drug in high concentrations specifically to the region of brain involved in producing seizures, then the therapeutic-to-toxic ratio might substantially be improved.

Investigators working with animal models of epilepsy have long delivered various putative anti-seizure medicines to different regions of animal brain, summarized in Table 2.

In 1997, Fisher and associates⁵⁶ showed that interictal spikes and seizures produced by the convulsant GABA-antagonist, bicuculline methiodide (BMI) applied to rat cortex could be reduced by local perfusion of diazepam (Figure 3).

Delivery of diazepam to a BMI-induced cortical seizure focus based upon an on-line seizure detection algorithm⁵⁷ can truncate seizures and prevent other seizures in a rat.

Diazepam is not itself a practical drug for perfusion on human brain, because of its alkalinity and depression of cardiorespiratory centers. Better candidates for focal brain perfusion to stop seizures include adenosine⁵⁸, muscimol⁵⁹ or pentobarbital⁶⁰. Greater penetration of perfused drug can be achieved by pressurizing the infusion catheter to produce bulk convection⁶¹.

Another strategy to distribute infused drug widely is to deliver it to the ventricular system. Serralta⁶² showed that continuous intracerebroventricular infusion of valproic acid in the rat suppressed seizures with minimal side effects. Oommen and the current author⁶³ showed efficacy against flurothyl-induced seizures after five days of gabapentin infusion into ventricles with an osmotic pump. A clinical trial of ventricular perfusion of antiepileptic medication is about to be started by ICVRx®. Safety and efficacy will need to be shown by clinical trials, and the ideal agent to use is not yet established.

Neurostimulation

Vagus nerve stimulation is currently the only approved stimulation therapy in the United States, but stimulation has been proposed at sites as varied as (see^{64,65} for citations) cerebellum, anterior thalamus, centromedian thalamus, subthalamic nucleus, hippocampus, caudate, locus coeruleus, corpus callosum, mammillothalamic tract and the cortical seizure focus.

Vagus and Peripheral Nerve Stimulation

Vagus nerve stimulation was approved in Europe in 1994 and in the United States and Canada in 1997 for therapy of epilepsy, based upon pivotal trials in patients with partial and secondarily generalized seizures in patients over 12 years of age⁶⁶⁶⁷⁶⁸. Retrospective studies of 440 patients implanted for 2–3 years⁶⁹ and for greater than ten years⁷⁰. VNS has been shown to be effective for partial and secondarily generalized seizures in pediatric populations⁷¹⁷²⁷³. Small trials⁷⁴ have suggested efficacy of VNS for some generalized seizures.

The clinical VNS device allows a noninvasive paddle held near the device to program current intensity, individual pulse duration, pulse frequency, on-off cycle time and intensity and duration of an extra pulse triggered by a magnet held over the stimulator. Tecoma and Iragui⁷⁵ reviewed value of varying these stimulation parameters. Pulse width of 0.25 ms may be better tolerated than those of 0.5, with similar efficacy, but 0.13 ms pulses are less effective. Stimulation at frequencies below 20 per second may allow increased stimulation of unmyelinated C-fibers, with more autonomic side effects. A controlled study of on-off cycle durations (DeGiorgio⁷⁶ showed no differences in efficacy; however, some non-responders improved when the on-cycle was later increased. No stimulation parameter set has yet been shown conclusively to be better than those used in the pivotal trials, recognizing that individual patients may respond to various parameter changes.

Vagus nerve stimulation technology continues to be under development. Size of the device is decreasing, such that the Demipulse device is smaller and has improved monitoring of battery life⁷⁷. High-field MRI has recently been shown safe, with a 3T GE Signa scanner using a specific T/R head coil⁷⁸, but more experience with safety is needed for other systems. Externally rechargeable devices are under development, so the battery need not be replaced every few years. Development of remote monitoring and telemedicine capabilities for the vagus stimulator is in progress. The ADNS-300 stimulator system⁷⁹ can record VNS compound action potentials, affording possible enhancement of understanding of the physiology of vagus stimulation for epilepsy and perhaps better individualization of stimulation parameters. Recording from the VNS also holds the possibility of early detection or even anticipation of seizures. In rats with pentylenetetrazol-induced tonic seizures⁸⁰, a measure of energy in the nerve could be used to predict behavioral seizures. Some patients benefit from using a magnet to turn VNS on at start of a seizure. A trial has begun at Ghent University in Belgium of using ictal tachycardia to trigger stimulation⁸¹.

One retrospective study⁸² found that unilateral interictal discharges, cortical dysplasia and younger age were predictive of better outcomes. However, most reviews have concluded that it is difficult to predict who will benefit from VNS⁷⁰⁷⁵. For that reason, external stimulation paradigms are of interest as noninvasive screens for whether an implanted stimulating device is likely to be of value. An auricular branch, called the Arnold nerve has been hypothesized to be a potentially useful test stimulation site prior to device implantation⁸³. A randomized study of electroacupuncture for pain effectively used stimulation at this superficial vagal auricular site⁸⁴. Transcutaneous stimulation of the left vagus nerve under the tragus of the ear was shown to influence MRI BOLD signals in the left locus coeruleus, left thalamus, left cingulate, left insula, left prefrontal cortex, and bilateral postcentral gyrus⁸⁵. DeGiorgio⁸⁶ used superficial stimulation of the supraorbital nerve to identify responders, who are implanted with a subcutaneous supraorbital nerve stimulator. In an unblinded paradigm, seizure frequency was reduced relative to baseline by 66% at 3 months, 56% at 6 months and 59% at 12 months. Efficacy will need to be validated in a larger controlled, blinded study.

Transcranial Magnetic Brain Stimulation

Electrical shocks to the scalp can activate cortical neurons, but the stimulation tends to hurt⁸⁷; transcutaneous magnetic stimulation (TMS) is less painful. Magnetic field induced brain currents fall off rapidly with distance from the magnetic stimulator coil, so great efforts have been made to produce coils that can stimulate focally and relatively deeply into brain tissue⁸⁸. Figure-of-eight coils are widely in use by virtue of these characteristics.

Early case series of TMS for epilepsy generally were favorable⁸⁹. Nine patients with partial or secondarily generalized seizures, two from temporal and seven from extra-temporal regions were given TMS⁹⁰. A round magnetic coil stimulated the vertex head region at one pulse every 3 seconds, for two trains of 500 pulses per day. Weekly seizure frequency declined from 10.3 ± 6.6 before stimulation to 5.8 ± 6.4 , significant at $p=0.048$. Subsequent case series of TMS showed benefit for seizures in some^{91,92,93,94,95} and little or no benefit in others^{96,97}. Positioning of the stimulating coil over the seizure focus might be important in determination of success, according to one study that compared vertex stimulation to targeted TMS⁹⁸.

Three controlled trials of TMS for epilepsy have been accomplished. In a positive trial, Fregni and associates⁹⁹ targeted TMS to sites of cortical dysplasia in 21 patients with medication-resistant seizures. Patients were subjected to five consecutive daily 20-minute sessions of stimulation at 1 per second, using either a figure-of-eight real stimulation coil or a fabricated coil looking and sounding similar to a real coil but delivering no stimulation. The epileptogenic focus was targeted as the site of stimulation, except in four patients with diffuse abnormalities, in whom stimulation was delivered to the vertex. By 2, 4 and 8 weeks after stimulation, seizure frequency was reduced respectively to 72%, 53% and 58% of baseline, each of which was statistically significant. EEG epileptiform discharges also were reduced. Two other controlled studies were negative. Cantello and associates¹⁰⁰ stimulated 43 patients with medication-resistant predominantly focal cortical epilepsies. After a 12-week baseline TMS was initiated via two stacked stimulating coils over the vertex. Active treatment was stimulation with the one near the scalp, and sham with stimulation by the upper coil distant from the scalp. Stimulation was set at two daily series of 500 stimuli at 0.3 Hz, separated by a 30-s interval. The stimulus intensity was 100% of the motor-evoked threshold. Although the study showed trends in favor of stimulation, neither seizure frequency nor EEG epileptiform activity changed significantly with active versus sham stimulation. Theodore and coworkers¹⁰¹ evaluated TMS in 21 patients with localization-related epilepsy. TMS was given at 120% of the motor-evoked threshold at 1 pulse per second for 15 minutes twice daily for 1 week at 120%. The coil was positioned over the best estimate of the region of the seizure focus. Sham stimulation was given with the coil angled away from the head. The patients were then observed on a stable drug regimen for two months. Neither partial nor generalized seizures improved significantly with TMS active stimulation in comparison to sham stimulation. A trend toward short-term benefit was noted in patients with lateral temporal seizure foci, where magnetic fields would best penetrate the focus.

Experience collectively leaves open the question of effectiveness of TMS for epilepsy. One of three controlled studies showed efficacy. That study targeted stimulation to superficial regions of cortical dysplasia, which may have been a factor in efficacy. Other differences in stimulation parameters, such as frequency, intensity, duration of the train and other factors could have contributed to different study outcomes. In addition, compared to other trials of neurostimulation, TMS trials have stimulated only during a small fraction of each trial day.

Magnetic stimulation is not entirely benign, in that it inadvertently can instigate seizures, even with single pulses¹⁰². A systematic literature review⁹⁴ found 16 cases of seizures with

TMS. This is a low percentage, given the thousands of patients exposed to TMS ¹⁰³. A consensus conference on safety of TMS ⁹⁴ concluded that TMS was contraindicated when metallic hardware, such as a cochlear implant or medication pump, was in close proximity to the stimulation site. Special care is required with untested stimulation parameters, patients with a seizure history or brain lesions or medications that lower seizure thresholds, or pregnancy or heart disease.

Thalamic Stimulation

The first devices used to treat epilepsy were forms of electrical stimulation. Electrical stimulation to map human brain function may have started in 1884, when the Cincinnati surgeon Robert Bartholow observed contralateral movements with electrical stimulation of cortex during repair of cranial osteomyelitis ¹⁰⁴. Wilder Penfield and Herbert Jasper pioneered the technique of mapping cortex with electrical stimulation, and Spiegel and Wycis of mapping and sometimes stimulating deep structures ¹⁰⁴; however, these investigators did not use stimulation as treatment. The first therapeutic brain stimulation efforts were in the field of psychiatry, by Heath ¹⁰⁵ and Delgado ¹⁰⁶ in the early 1950's. Some of Heath's patients had epilepsy as well as psychiatric problems, and epileptiform spikes were observed at septal nuclei and other stimulation sites ¹⁰⁵.

Deep brain electrical stimulation to reduce seizures is credited to the New York Neurosurgeon, Irving Cooper, who reported improvement in seizure frequency with stimulation either of cerebellum ¹⁰⁷ or the anterior thalamus ¹⁰⁸. Cooper's positive results were qualitative and uncontrolled with little detail on individual degrees of improvement and comorbid conditions. In subsequent years, about a dozen uncontrolled studies showed benefit of cerebellar stimulation to treat epilepsy, but two small blinded studies were negative ¹⁰⁹. DBS for epilepsy fell out of favor for many years and came back to interest with the success of vagus nerve stimulation for epilepsy and DBS for movement disorders. After cerebellum, centromedian thalamus was the primary target of stimulation, pioneered by the Velasco's in Mexico City ¹¹⁰¹¹¹, but a small cross-over trial was negative ¹¹².

A series of studies showed benefit of DBS of anterior thalamus in experimental models of epilepsy ¹¹³. Based upon promising animal experimentation and the early work of Cooper, six small unblinded trials of anterior nucleus stimulation for medication-resistant epilepsy were published ⁶⁴, showing a conglomerate mean 47% reduction in seizures compared to baseline. Uncontrolled stimulation studies are subject to several types of potential bias, including placebo effect, regression to the mean, micro-lesion effects from electrode placement and other unknown confounding factors. Therefore, Fisher and associates ¹¹⁴ performed a randomized, placebo-controlled, multi-center trial of anterior nucleus stimulation in patients with medication-resistant partial and secondarily generalized seizures, called SANTE, for stimulation of the anterior nucleus of thalamus for epilepsy. Randomization was performed on 110 patients either to 5 V or 0 V (placebo) stimulation of bilateral anterior nuclei of thalamus, at 145 pulses per second, 0.9 ms pulses referential to the stimulation case, with stimulation on for 1 minute and off for 5 minutes. The group had a median of about 20 seizures per month and a mean of 57 seizures per month at baseline. Stimulation was begun one month after implantation of the deep brain leads, and continued for a three-month blinded phase. Figure 4 shows seizure frequency relative to baseline.

Seizure frequency declined 20% in the month after implantation prior to initiation of electrical stimulation, either to nonspecific or micro-lesion effects. By the end of the blinded phase, the treated group continued to improve, to a median level 40.5% less than baseline, compared to only 14.5% in the 0 V group ($p=0.038$). The control group received 5V stimulation at the end of the blinded phase. Seizures declined over the next two months to levels encountered in the initially stimulated group. Improvement was sustained, with

seizures in the terminal three months of stimulation at three years measuring a median 58% reduction compared to baseline. In the blinded phase, stimulation produced significant reduction in injuries due to seizures, frequency of complex partial seizures, seizures originating from the temporal lobes and seizures pre-designated as “most severe” by the patient. Responder rates for 50% improvement and quality of life did not significantly improve during the three-month blinded phase, but did in the open-label and long-term follow-up stages from 1 to 3 years after implantation. In the long-term phase, 14% of patients became seizure-free for at least 6 months. Patients who previously had not benefitted from vagus nerve stimulation or epilepsy surgery had the same favorable response to DBS as did the overall group.

Complications of stimulation consisted of occasional chest or other paresthesias, need for repositioning leads, and superficial infections. No symptomatic brain hemorrhages were seen, though neuroimaging showed asymptomatic blood in five patients. Neuropsychological tests showed no difference in cognitive or profiles of mood scores, but more stimulated patients reported symptoms of depression and memory impairment. Five patients had status epilepticus, two related to initiation of stimulation, and resolving with reduction of voltage. Rates of depression, status epilepticus, depression, suicide and sudden unexpected death in epilepsy (SUDEP) all were within the expected ranges for a population of people with refractory epilepsy.

The conclusion of the SANTE study was that stimulation of the anterior nuclei of thalamus reduced the number of seizures in patients with medication-resistant epilepsy. Complications were similar to those encountered with DBS for movement disorders, with additional concerns raised about possible subjective symptoms of depression and memory impairment.

Responsive Neurostimulation

A second randomized trial of neurostimulation employed a strategy to stimulate subdural strips or depth electrodes placed near seizure foci, in response to electroencephalographically-detected epileptiform activity¹¹⁵. A total of 191 patients with medication-resistant partial or secondarily generalized seizures were implanted with a responsive neurostimulator (RNS) affixed within a craniotomy, and connected subcutaneously to a subclavicular stimulator (Fig. 5).

Patients were randomized to receive active or sham stimulation. Stimulation was begun one month after implantation, and the three-month blinded test phase began two months after implantation. Improvement was similar to that seen in the SANTE study, with 37.9% mean change in seizure frequency relative to baseline for the actively stimulated group, versus 17.3% in the sham stimulated group, significant by generalized estimating equations at $p=0.012$. In the third month of the blinded evaluation period, the reduction in seizures in the treatment group reached 41.5% and in the sham stimulation group was 9.4% ($p = 0.008$). The seizure reduction was sustained, and even improved, over time. The median % reduction in seizures and responder rates at 1 year were 44% each and at 2 years were 53% and 55%. There were statistically significant improvements in overall quality of life (QOL) and in 9/16 QOLIE-89 scales at 1 and 2 years after implantation. There was no deterioration in any neuropsychological measure and there were statistically significant improvements at 1 and 2 years post-implant in verbal function, visual-spatial processing, memory and mood. Stimulation was well-tolerated.

At the time of this writing, based upon the SANTE trial, DBS is approved for clinical use in Europe and several other countries, but the US FDA is still evaluating the risk-benefit balance. The RNS System is under evaluation by the US FDA. Is a median 40% improvement in seizures (during the blinded phase) sufficient to justify the risks of

implanted stimulators? Each patient and clinician will ultimately need to individualize this answer. However, improvements in this range can be clinically meaningful, especially where all else has failed, and when some improve markedly with stimulation. Experience is currently insufficient to recommend when to use thalamic or responsive neurostimulation in relation to vagus nerve stimulation. The latter clearly is less invasive. Responsive stimulation requires knowing where to place the stimulators. Clinical trials are underway for hippocampal stimulation and testing at other CNS sites are in planning.

Conclusion

Therapeutic devices to treat epilepsy described in this review represent an incomplete list. Some devices may come to the bedside and others will be found ineffective, too invasive or too difficult to implement. Clinical trials of devices are more problematic than are medication trials. Medical devices are expensive, although not necessarily more expensive than chronic therapy with some drugs. Nevertheless, devices can provide clinically meaningful benefits in people who have failed less invasive therapies. Devices are not curative, and as such, device therapy will serve as an important bridge to the time when we can prevent and cure epilepsy.

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Figure 1.

A. A Peltier cooling device (cool side down) is situated over a left frontal seizure focus in an anesthetized rat. The seizure focus was induced by placement of the GABA antagonist, bicuculline methiodide 2 mM. **B.** Upper panel shows spikes at 37° C. The middle panel shows attenuation of spikes with cooling of cortex. The lower panel shows reversible return of spiking with rewarming to 37° C.

Figure 2.

A. In an organotypic hippocampal culture, a yellow-orange light (marked by orange bar) activates channel rhodopsin, opens chloride channels, hyperpolarizes transfected neurons and inhibits firing. **B.** Stimulus-train-induced bursting in hippocampal culture slices is inhibited by halorhodopsin mediated response to orange light (marked by orange bar, middle panel). Region of expanded insets is marked by dotted rectangles. Adapted with permission from Tønnesen et al.⁴⁵.

Figure 3.

A. The GABA antagonist drug, bicuculline methiodide 4 mM, is placed via cannula a twist drill skull opening onto the left parietal cortex of an anesthetized rat. Bone screws record EEG at left anterior (LA), right anterior (RA), left mid-cortex (LM), right mid-cortex (RM), left parietal (LP) and right parietal (RP) with respect to a reference (Ref) over the frontal midline sinus. **B.** Bipolar EEG at baseline. **C.** Epileptiform spikes are seen over the LM electrode after placement of bicuculline methiodide (BMI) 4 mM. **D.** Epileptiform spiking disappears seconds after administration of diazepam via the catheter. Adapted with permission from Eder et al. Eder ⁵⁶.

Figure 4. In the SANTE trial of anterior nucleus stimulation, patients receiving active stimulation (green solid line) have fewer median seizures as a percentage of baseline than do those receiving sham stimulation (red dashed line). Adapted with permission from Fisher et al.¹¹⁴.

Figure 5. Diagrammatic view of a responsive neurostimulator implanted in right temporal skull, with a recording-stimulating strip over the right frontal region and a stimulating-recording depth wire in the right occipital region. With permission, courtesy of Martha Morrell of NeuroPace®.

Table 1

Methods to predict seizures

➤	Recent seizure in patients whose seizures tend to cluster
➤	Known seizure precipitants
➤	Patient awareness
➤	Blood flow changes
➤	EEG component frequency analysis
➤	EEG nonlinear “chaos theory”
➤	Energy bursts
➤	Entropy
➤	EEG synchronicity and correlation
➤	EEG high-frequency oscillations
➤	Multiple unit response
➤	Other

Table 2

Laboratory studies of drug perfusion for seizures

Study	Agent	Epilepsy model	Target	Finding
Antonucci et al. 2009 ⁴⁶	botulinum neurotoxin e	chronic seizures from kainic acid into rat hippocampus	hippocampus	decreased spontaneously recurrent seizures
Chapman et al. 1999 ⁴⁷	R,S-4-phosphonophenylglycine, a metabotropic glutamate antagonist	auditory seizures in genetically prone rats	inferior colliculus	inhibited sound- induced seizures
Dean and Gale 1989 ⁴⁸	bicuculline (disinhibition)	maximal electroshock in rat	rostralateral superior colliculus	inhibited seizures
Gallego et al. 2009 ⁴⁹	GABA	amygdala kindling in rat	dorsomedian thalamus	elevated threshold for generalized seizures
Gasior et al. 2007 ⁵⁰	omega-conotoxin N- type calcium channel blockers	amygdala-kindled seizures in rats	amygdala	prolonged attenuation of seizures
Myhrer et al. 2006 ⁵¹	ethanol, propofol, muscimol, diazepam	soman seizure in rats	substantia nigra or area tempestas	seizure inhibition
Myhrer et al. 2010 ⁵²	various metabotropic glutamate antagonists	soman seizure in rats	perirhinal cortex	increased latency to or protected against seizures
Sayyah et al. 2007 ⁵³	all-trans retinoic acid	amygdala-kindled seizures in rats	amygdala	inhibits kindled seizures
Silva-Barrat et al. 1988 ⁵⁴	GABA	allylglycine-induced seizures in baboon	motor cortex, reticular magnocellular nucleus, substantia nigra	reduced photosensitive seizures
Smith et al. 1993 ⁵⁵	lidocaine	bicuculline in rat	prepiriform cortex	reduced duration and severity of seizures