Emerging devices for epilepsy

Chrystal Marie Reed, MD, PhD

Michael Gruenthal, MD, PhD

Summary

About 30% of people with epilepsy continue to have seizures despite a growing array of antiseizure drugs. For some of these people, surgical resection of brain tissue is an effective therapeutic option. For others, the likelihood of seizure freedom is low, and has not improved much despite the introduction of several new antiseizure drugs. The vagus nerve stimulator is the only device approved by the Food and Drug Administration (FDA), but it rarely results in freedom from seizures. Recently, 2 approaches to electrical stimulation of the brain have been reported. One device has been approved for use in Canada and in Europe, and it seems likely that one or more such devices will be approved for use in the United States. We examine some of the data from these studies in the context of the current FDA-approved drugs and devices.

In their 1938 article describing the anticonvulsant effect of sodium diphenyl hydantoinate (phenytoin) in people with epilepsy, Merritt and Putnam¹ begin by stating: “Good results in the treatment of patients with convulsive seizures have been obtained by a variety of methods, such as medical treatment with bromides or barbituric acid compounds, the ketogenic diet, restriction of fluids, and the surgical excision of scars or irritable cortical foci. In spite of these various therapeutic means there are a great number of patients who are not relieved of their attacks or are helped only temporarily by treatment.”

The importance of the approach pioneered by Merritt and Putnam, namely, the selection of candidate compounds on the basis of molecular structure and screening in animal models, cannot be overstated. Many people with epilepsy have benefitted from the treatments introduced in the subsequent 75 years. Nevertheless, the similarity between Merritt and Putnam’s assessment and the current state of epilepsy therapy is a sobering reminder that our progress has been slow and incremental.

While most neurologists know specific people with epilepsy whose lives have improved substantially, treatments introduced in the past few decades have not had a significant effect

Department of Neurology, Albany Medical College, Albany, NY.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp.**

Correspondence to: gruentm@mail.amc.edu

While most neurologists know specific people with epilepsy whose lives have improved substantially, treatments introduced in the past few decades have not had a significant effect on the likelihood of seizure freedom.

on the likelihood of seizure freedom.² The results of studies designed to assess seizure control with available antiseizure drugs published between 1985³ and 2012⁴ show many more similarities than differences, with the likelihood of seizure freedom remaining just below 50% with initial monotherapy and improving to about 70% with subsequent monotherapy or polytherapy.

There are many potential explanations for this lack of progress, including the manner in which potential antiseizure drugs are screened and selected and the less than adequate understanding of the pathophysiologic bases for the heterogeneous conditions that we collectively call epilepsy. These important issues are beyond the scope of this review.

Medical devices

The vagus nerve stimulator Against this backdrop of suboptimal progress, the therapeutic potential of stimulation-based therapies is being investigated. The only Food and Drug Administration (FDA)–approved device thus far is the vagus nerve stimulator (VNS), an implanted extracranial device that delivers intermittent biphasic current to the left vagus nerve. This device cycles on and off repeatedly at a programmable stimulation interval, duration, intensity, pulse width, and frequency. Passing a magnet near the skin overlying the device can trigger additional stimulations. The regulatory trials demonstrated a statistically reliable reduction in seizure frequency in some patients.⁵ Unfortunately, the likelihood of seizure freedom associated with the VNS is less than 10%.^{6,7}

Opportunities to improve the efficacy of the VNS have been proposed, including a suggestion that extracerebral signals such as ictal tachycardia could be used to detect seizure onset and trigger the VNS or a similar device.⁸ The potential advantages of such an approach include lower cost and less surgical risk than intracranial surgery. The potential disadvantages include applicability limited to patients with ictal tachycardia and, based on experience with magnet activation of the VNS, the likelihood that efficacy would be limited to a subset of those patients. Because the existing VNS models lack this capability, a new model would need to be developed and tested.

Trigeminal nerve stimulation Based on the notion that cranial nerve stimulation causes widespread cortical desynchronization, a phase II study designed to investigate external trigeminal nerve stimulation was reported in 2013.⁹ The study participants were 50 patients with drug-resistant partial onset epilepsy with 2 or more complex partial or secondarily generalized tonic-clonic seizures per month despite at least 2 antiseizure drugs. After a 6-week baseline, patients entered an 18-week treatment period during which trigeminal nerve stimulation was provided by an external device through bipolar transcutaneous gel-based electrodes designed to stimulate bilateral branches of the ophthalmic and supra-trochlear nerves. In this double-blind study, patients were randomized to treatment (high intensity) or active control (low intensity) groups. Twenty-three of the 25 patients from the treatment group and 19 of the 25 patients from the active control group completed the study. There was a significant within-group improvement in the responder rate for the treatment group after 18 weeks. Changes in responder rates and median % change in seizure frequency between the treatment and active control groups were not significant.

Trigeminal nerve stimulation was well-tolerated. Treatment-related adverse events were mainly skin irritation, anxiety, and headache. On the basis of this and some suggestion of efficacy, the authors describe plans for a larger phase III multicenter study.

Electrical stimulation of the brain The effect of chronic electrical stimulation of the cerebellum in people with epilepsy was reported in 1973.¹⁰ The commercial availability of implantable chronic intracranial electrodes and extracranial control devices for the treatment of movement disorders has facilitated the opportunity to explore strategies for detecting seizure onset via intracranial electrodes or preventing seizures by electrical stimulation of the brain. Robust clinical trial data are available for 2 approaches: a closed-loop or “responsive” system that delivers an electrical stimulus when a seizure is detected and an open-loop system in which scheduled stimulation is delivered at regular intervals.

Cortical stimulation in response to detected seizures The results of a multicenter trial designed to investigate the safety and effectiveness of “responsive” cortical electrical stimulation were published in 2011.¹¹ This double-blind, randomized, active vs sham-stimulated controlled trial was available to adults with partial-onset seizures with 1 or 2 identified epileptogenic regions who reported at least 3 seizures per month while taking at least 2 antiseizure drugs. Participants underwent surgical implantation of the NeuroPace, Inc., intracranial responsive cortical stimulator with 1 or 2 depth or subdural electrodes placed in the previously identified epileptogenic regions. The device was programmed to deliver electrical stimulation when abnormal electrocorticographic activity was detected. Participants were assigned at random to receive active treatment or sham stimulation. During a subsequent open-label period, all participants received active treatment.

After a 4-week period in which seizure detection and stimulation parameters could be optimized by a nonblinded physician, participants entered a 12-week blinded evaluation period. In the first month of the blinded evaluation period, the treatment group had a 34.2% reduction in seizure frequency compared to a 25.2% reduction in the sham-stimulated group. The reduction in seizure frequency in the sham group was not sustained during the remainder of the blinded period, and by the end of the blinded period the treatment group had a 37.9% reduction in seizure frequency compared to 17.3% in the sham-stimulated group.

Two treatment group participants (2.1%) and none of the sham-stimulated participants were seizure-free during the 12-week blinded evaluation period. When participants from the sham group entered the open-label extension and received unblinded treatment, they also experienced a significant reduction in seizure frequency. The quality of life scores for both groups showed statistically significant improvement that was similar at the end of 1 year. During the final 12 weeks of data collection, 7.1% of participants who remained in the study were seizure-free.

The reduction in seizure frequency associated with stimulation was not dependent on type of epilepsy, the number of seizure foci, or previous VNS or resective epilepsy surgery. The risk of serious adverse events including hemorrhage and infection was not greater than those associated with epilepsy surgery or deep brain stimulation implantation for movement disorders.

Periodic thalamic stimulation The results of a multicenter trial designed to investigate the safety and effectiveness of open-loop stimulation of the anterior nuclei of thalamus for epilepsy (SANTE) were published in 2010.¹² This stimulation target was chosen based on extensive projections to frontal and temporal cortex and promising data from several smaller studies. The specific antiseizure mechanism is unknown. This double-blind, randomized controlled trial was available to adults with partial-onset seizures who reported at least 6 seizures per month and inadequate seizure control from at least 3 antiseizure drugs. All participants underwent surgical implantation of bilateral thalamic anterior nucleus stimulating electrodes. One month later, they were randomly assigned to receive either

Unfortunately, it appears that the likelihood of seizure freedom from these devices may be disappointingly low, with only around 10% of the eligible patient population reaching that therapeutic milestone.

stimulation for 1 minute every 5 minutes or no stimulation. After a 12-week blinded phase, all participants received stimulation during a 36-week unblinded phase during which limited adjustment of the stimulation parameters was permitted. During a subsequent long-term follow-up, any safe adjustment to the stimulation parameters and medication was permitted.

Differences in seizure frequency between the stimulated and control groups began to emerge 1 month after stimulation began. At the end of the 3-month blinded phase, there was a 40.4% reduction in median seizure frequency in the stimulated group and a 14.5% reduction in the control group, a statistically significant difference. During the open-label phase with both groups receiving stimulation, there was 41% reduction in median seizure frequency at 13 months and a 56% reduction at 25 months. A total of 12.7% of participants were seizure-free for at least 6 months.

The most common device-related adverse event was paresthesias, reported by 18.2% of participants. Status epilepticus was reported in 5 patients (4.5% of participants). Two of these patients were receiving stimulation at the time of status epilepticus. Unlike the closed-loop cortical stimulation trial, subgroup analyses suggested that patients with temporal lobe seizure onset had greater benefit from bilateral thalamic stimulation than those with extratemporal seizure onset.

The results of these studies are encouraging; they validate the concept of brain electrical stimulation as a feasible therapy and suggest that some people with epilepsy who match the characteristics of the study participants will benefit.

Unfortunately, it appears that the likelihood of seizure freedom from these devices may be disappointingly low, with only around 10% of the eligible patient population reaching that therapeutic milestone. Unless refinement of stimulation parameters increases the likelihood of seizure freedom, it seems that resective epilepsy surgery will remain the most effective therapeutic option for eligible people with epilepsy who do not respond to antiseizure drugs. These studies were designed to meet regulatory requirements for demonstrating safety and efficacy. While historical evidence makes it unlikely that the addition of another medication would be effective in this population, the lack of a medication arm prevents a direct comparison of the benefit of these devices vs adding another medication.

The thalamic stimulation device manufactured by Medtronic Inc. is approved in Canada and in Europe. A 2010 FDA advisory panel recommendation for approval was not upheld due to concerns regarding the length of the blinded phase of the study. The FDA has not announced whether or not to uphold a 2013 advisory panel recommendation to approve the NeuroPace device.

Unanswered questions

As we enter an era of expanding nonpharmacologic therapeutic options, many questions remain unanswered. When people with epilepsy do not respond to antiseizure drugs, how will we make rational recommendations about which of the growing array of device therapies to try? Without an understanding of the neurobiological (or even phenomenological) basis for why people do or do not respond to a particular therapy, how can we match each patient with

Take-home points

- Thirty percent of people with epilepsy are not seizure-free with currently available treatments.
- The likelihood of seizure freedom has not increased substantially despite the introduction of many antiseizure drugs and the vagus nerve stimulator.
- Direct electrical stimulation of the brain is an emerging treatment option.
- Two recent trials suggest that a closed-loop cortical stimulation device and an open-loop thalamic stimulation device are safe and effective.
- The likelihood of seizure freedom from these devices appears low.

the most effective treatment? Absent a detailed understanding of the specific antiseizure mechanisms induced by various devices, might we miss specific drug/device combinations that are particularly effective? How will cost, safety, and effectiveness constraints based on heterogeneous populations limit access to these therapies for those undefined subgroups likely to benefit the most? How will safety concerns regarding MRI affect subsequent care for people who may require cranial or extracranial imaging?

Ultimately, the answers to some of these questions and the potential “real-world” value of these new therapies may become clearer with clinical experience. Nevertheless, if we consider successful treatments to be those resulting in freedom from seizures, the data from these studies suggest that most people with epilepsy not currently controlled will be disappointed. We should be prepared for the possibility that, absent a complete understanding of the neurobiology of epileptogenesis and ictogenesis, major therapeutic breakthroughs may not be possible.

REFERENCES

1. Merritt HH, Putnam TJ. Sodium diphenyl hydantoinate in the treatment of convulsive disorders. *JAMA* 1938;111:1068–1073.
2. Brodie MJ. Antiepileptic drug therapy: the story so far. *Seizure* 2010;19:650–655.
3. Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med* 1985;313:145–151.
4. Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. *Neurology* 2012;78:1548–1554.
5. The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. *Neurology* 1995;45:224–230.
6. Ghaemi K, Elsharkawy AE, Schulz R, et al. Vagus nerve stimulation: outcome and predictors of seizure freedom in long-term follow-up. *Seizure* 2010;19:264–268.
7. Elliott RE, Morsi A, Kalhorn SP, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. *Epilepsy Behav* 2011;20:57–63.
8. Osorio I, Schachter S. Extracerebral detection of seizures: a new era in epileptology? *Epilepsy Behav* 2011;22(suppl 1):S82–S87.
9. DeGiorgio CM, Soss J, Cook IA, et al. Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy. *Neurology* 2013;80:786–791.
10. Cooper IS, Amin I, Gilman S. The effect of chronic cerebellar stimulation upon epilepsy in man. *Trans Am Neurol Assoc* 1973;98:192–196.
11. Morrell MJ. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology* 2011;77:1295–1304.
12. Fisher R, Salanova V, Witt T, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia* 2010;51:899–908.

STUDY FUNDING

No targeted funding reported.

DISCLOSURES

C.M. Reed reports no disclosures. M. Gruenthal serves as a consultant to the New York State Department of Health, receives research support from Eisai Inc., Sunovion, and Upsher-Smith Laboratories Inc., and receives royalty payments from Apple, Inc. for computer software. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

Related articles from other AAN physician and patient resources

Continuum: Lifelong Learning in Neurology® ● www.ContinuumJournal.com

Surgical treatment of epilepsy

June 2013;730-742.

Neurology Now® ● www.neurologynow.com

This way in: Reducing seizures with brain stimulation

February/March 2012;8:8-9.

Neurology Today® ● www.neurotodayonline.com

Five years after DBS, epilepsy outcomes improved

January 3, 2013;13:1, 5-7.