Responsive Direct Brain Stimulation for Epilepsy

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KEYWORDS

• Closed-loop • Responsive • Stimulation • Epilepsy • Intractable • Intracranial • Electrocorticogram • Neurostimulator

KEY POINTS

- Closed-loop responsive stimulation of the seizure focus reduces the frequency of medically intractable partial onset seizures from 44% at 1 year to 60% to 66% over 3 to 6 years of treatment.
- Risks of responsive stimulation as provided by the first responsive neurostimulator (RNS System) are similar to other implanted medical devices, and the neurostimulator can be programmed so that therapeutic stimulation is not perceived.
- There are improvements in quality of life with responsive stimulation and no negative effects on mood or cognition, and some patients experience improvements in aspects of language and memory.
- Quantitative electrophysiological data combined with clinical seizure counts are used to establish optimal detection and stimulation settings for each patient.
- Chronic ambulatory electrocorticographic monitoring provides information regarding the location(s) of the seizure focus and may provide biomarkers to measure disease activity.

INTRODUCTION

Neurostimulation is an increasingly important treatment modality for disorders of the nervous system.[1–4] Most neurostimulation devices are open-loop; stimulation settings are preprogrammed and do not automatically respond to changes in electrophysiological signals or the patient's clinical symptoms. Open-loop stimulation is effective in several clinical applications, including Parkinson's disease,[5,6] essential tremor,[7] dystonia,[8] pain,[9] and more recently, epilepsy.[10,11] However, because many neurologic disorders are not static conditions, there is increasing interest in neurostimulation approaches that adapt to changes in clinical symptoms or quantitative biomarkers.

In contrast to open-loop stimulation devices, responsive (or closed-loop) neurostimulation devices modulate or adapt therapy in response to physiologic signals, in addition to clinically overt symptoms, and may be more efficient, effective, and better tolerated than open-loop stimulation.[12,13] Responsive stimulation approaches are being explored for Parkinson's disease. Investigational closed-loop stimulation for Parkinson's disease provides stimulation in the subthalamic nucleus in response to changes in beta amplitude, with reports of improvements in motor function, speech, gait, and balance.[13–18]

This review focuses on targeted cortical responsive stimulation, which has been approved by the US Food and Drug Administration (FDA) for the

Disclosures: Dr M.J. Morrell is an employee of and has equity ownership/stock options with NeuroPace Inc. Dr C. Halpern does not have any conflicts of interest that are relevant to the subject matter or materials discussed in this article.

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Neurosurg Clin N Am 27 (2016) 111–121
http://dx.doi.org/10.1016/j.nec.2015.08.012
1042-3680/16/$ – see front matter

adjunctive treatment of epilepsy with partial onset seizures.

NEUROSTIMULATION FOR EPILEPSY

Epilepsy comprises a group of neurologic conditions characterized by recurrent seizures. The partial epilepsies (also known as localization-related epilepsy) are the most common type of epilepsy in adults, and at least one-third cannot achieve seizure control with antiepileptic medications.[19] One option for these patients is to resect the seizure focus.[20,21] However, many patients with partial onset seizures are not candidates for a cortical resection because the chance of a substantial seizure reduction is too low or the risk of a neurologic morbidity is too high. Moreover, not all patients who undergo resective procedures achieve seizure freedom. Approximately 30% to 40% of patients who undergo temporal lobectomies, which is the most common and most successful type of resective surgery, continue to have disabling seizures at 1 year after surgery.[20–22]

Neurostimulation is an option for some patients with medically intractable partial seizures who have either failed or are not candidates for resective surgery. There are currently two FDA-approved neurostimulation therapies for adjunctive treatment of medically intractable partial-onset epilepsy: vagus nerve stimulation (VNS) and responsive cortical stimulation. A third neurostimulation modality, open-loop deep brain stimulation of the anterior thalamic nucleus, is not approved in the United States as of the date this is written, but is approved in other countries.[11]

The VNS Therapy System (Cyberonics, Houston, TX, USA)[23] provides open-loop scheduled stimulation to the vagus nerve using a pectorally implanted pulse generator and electrodes wrapped around the left vagus nerve. Stimulation is typically delivered for 30 seconds every 5 minutes. External application of a magnet over the pulse generator triggers additional stimulation.

Average seizure reductions in patients with intractable partial onset seizures during the blinded period of randomized controlled trials of the VNS Therapy System were 24% to 28%[24,25] and were 35% to 44% at 2 years in open-label prospective studies.[26] Side effects related to stimulation of the vagus and recurrent laryngeal nerve include voice alteration (50%), increased coughing (41%), pharyngitis (27%), dyspnea (18%), dyspepsia (12%), nausea (19%), and laryngismus (3.2%).[24,27] A recently FDA-approved VNS model (Aspire SR; Cyberonics, Inc) activates stimulation when the heart rate exceeds a prespecified threshold in order to provide additional treatment for seizures that are accompanied by tachycardia (Aspire SR, Cyberonics, Inc).[23] It is unclear at this time if this device will prove to be more efficacious or better tolerated than its open-loop precursor.

A reduction in seizures has been reported in several small and uncontrolled studies of open-loop continuous or scheduled neurostimulation as well as in one randomized controlled trial.[28] Stimulation targets have included the cerebellum,[29] caudate nucleus,[30–32] centromedian nucleus,[31,33,34] subthalamic nucleus,[35] and hippocampus.[36–38] In the only randomized controlled trial of open-loop stimulation,[10] 110 adults with medically intractable partial onset seizures were randomized to scheduled or sham stimulation in the anterior nuclei of the thalamus on a schedule of 1 minute on and 5 minutes off. Patients treated with stimulation had a significantly greater reduction in seizures compared with the sham stimulation patients with an overall adjusted percent difference of −17% ($P<.039$).[10] The stimulated group had significantly more adverse events related to depression, memory, and concentration, but there were not differences between the groups by neuropsychological testing. The seizure reduction at 1 year was −41% and reached 57% to 65% in years 3 through 5.[10,11]

Closed-Loop Responsive Direct Brain Stimulation

Closed-loop responsive direct brain stimulation represents a new treatment paradigm for epilepsy. Seizures and epileptiform activity are sporadic and relatively infrequent, making an episodic treatment approach such as responsive stimulation an attractive option. Clinical observations and small studies have shown that electrographic seizures induced by electrical stimulation during brain mapping can be shortened or even terminated by immediately delivering a brief burst of electrical stimulation at the site of the discharge.[39–41] Other small studies in persons being evaluated with intracranial electrodes for epilepsy surgery have indicated that automated stimulation to the seizure focus delivered by investigational external devices was well tolerated and seemed to suppress electrographic and perhaps clinical seizures.[42–44]

The Responsive Neurostimulator System

The first implantable closed-loop responsive direct brain neurostimulator was approved in the United States in late 2013 as an adjunctive therapy in adults with medically uncontrolled partial onset seizures localized to 1 or 2 epileptogenic foci.[45]