

The use of Neurostimulation for the Treatment of Drug-Resistant Epilepsy in Children

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Epilepsy is one of the most devastating conditions to potentially affect children. This condition, in which there is an enduring predisposition to future unprovoked epileptic seizures, is estimated to affect more than 300,000 children under the age of 15 in the United States alone. Approximately 60-70% of such children will be rendered seizure free with either the first or second anti-seizure drug tried [1]. However, 30-40% of these children will continue to suffer from epileptic seizures despite such medications [2]. By the time a third anti-seizure drug is tried, the chances of a child achieving complete seizure cessation drops to 5%. This becomes precipitously

less as more and more anti-seizure drugs are prescribed. Uncontrolled seizures have the potential to cause significant morbidity (including injuries from seizures, developmental delay/intellectual disability, and social isolation) and even mortality (including from status epilepticus and Sudden Unexpected Death in Epilepsy, SUDEP).

Given the unlikelihood of further medication trials rendering such children seizure free (and likely only exposing them to side effects from polypharmacy), it is imperative for physicians treating these children to explore other treatment options. For children with possible focal (i.e. partial) onset seizures, full workups should be performed to determine if they are candidates for Resective Epilepsy Surgery (RES). The superior efficacy of this treatment option versus continued medical therapy alone has been demonstrated in numerous trials, including two randomized controlled trials of patients with drug-resistant temporal lobe epilepsy [3,4]. Unfortunately, not all children will be appropriate candidates for such an intervention. Currently, children with medically intractable generalized and multifocal seizures are typically not considered for RES. In addition, if children have focal onset seizures arising from eloquent cortex (e.g. expressive/receptive language areas), RES might cause significant postoperative deficits, making the treatment worse than the

disease itself. For such children, physicians need to think outside of the box with regards to how to treat their seizures and improve their overall qualities of life.

Many of the newer treatments for Drug-Resistant Epilepsy (DRE) involve neurostimulation. Such devices include Deep Brain Stimulation (DBS), Responsive Neurostimulation (RNS), Trigeminal Nerve Stimulation (TNS), and Vagus Nerve Stimulation (VNS). Although many are still experimental in the United States, such devices have the potential to significantly improve the seizure-burden of children with DRE. Given that these devices work in ways unique to anti-seizure drugs, such efficacy often comes without significant side effects, further improving quality of life.

Although it is widely recognized for the treatment of movement disorders such as Parkinson's disease, the use of DBS in DRE has also been explored. In DRE, the target of such stimulation is usually the anterior nucleus of the thalamus. The anterior nucleus of the thalamus is a relay in Papez circuit, a key pathway involved in memory. This circuit is also involved in the propagation of some seizure types such as limbic seizures. Therefore, it has been hypothesized that repetitive stimulation of this pathway could serve to disrupt such seizures [5]. In a double-blind, randomized trial of 110 patients with medically-intractable focal onset seizures, bilateral stimulation of the anterior nuclei of the thalamus was demonstrated to significantly reduce seizures. Within 3 months, the group receiving stimulation experienced a 29% greater reduction in seizures versus the control (non-stimulated) group [6]. Such efficacy only improved with time. By 2 years, the majority (54%) of patients had achieved a seizure reduction of at least 50% (considered the gold

standard in new anti-seizure treatment trials). This included 14 patients who reported complete seizure freedom for at least 6 months [6]. However, DBS for DRE was not without risks. Intracerebral hemorrhage (albeit asymptomatic in all cases) was noted in 4.5% of patients, with an additional 12.7% experiencing device-related infections. The device did not improve mood in study subjects like some other forms of neurostimulation; in fact, 11% noted worsening of mood/depression. Five deaths were also reported during the study period [6]. Given these side effects (and the fact that its efficacy is not dramatically different than other forms of neurostimulation such as VNS), the likelihood of FDA approval of DBS for DRE is currently uncertain.

For children with medically intractable focal onset seizures who are not candidates for resective surgery, RNS may be a viable option. RNS involves the implantation of depth or strip electrodes over the region of seizure onset. After detecting brainwave activity suspicious for an epileptic seizure, the device delivers electrical stimulation to the site. Such tailored stimulation is designed to normalize electrical activity and either prevent seizure symptoms altogether or prevent progression to more severe symptoms (e.g. loss of consciousness, secondarily generalized tonic clonic seizures). In a double-blind, randomized controlled trial of 191 patients with medically refractory focal onset seizures, a 20.6% greater reduction in seizures was detected at 3 months in those receiving stimulation versus controls [7]. During the subsequent open-label period, the percentage of patients experiencing a 50% or greater reduction in seizures increased to 54% [7]. Side effects included infection (3.7%), increased seizures (5.7%), and six deaths (1 from suicide, 1 from lymphoma, and 4

from SUDEP) [7]. RNS received FDA pre-market approval in November 2013.

Another (less invasive) device that is being explored for the treatment of DRE is TNS. This device consists of non-invasive adhesive pads worn over the trigeminal nerves (typically the ophthalmic branches) which are connected to an external battery pack. In a double-blind randomized active-control trial of 50 patients with medically intractable focal onset seizures, repetitive stimulation of the trigeminal nerve was shown to increase rates of seizure reductions. Although not significant, there was a trend towards higher responder rates in patients receiving treatment versus active controls (30.2% versus 21.1% at 18 weeks, $p=0.31$) [8]. However, there was a statistically significant improvement in responder rate over time within the group receiving treatment (17.8% at 6 weeks versus 40.5% at 18 weeks, $p=0.01$) [8]. In addition, usage of TNS has been suggested as a possible non-pharmacologic therapy in the treatment of major depressive disorder [9]. Although the exact mechanism of action of TNS (and by extension VNS) is not currently known, many theories abound. These include desynchronization of Electro Encephalo Gram (EEG) rhythms [10] and increased cerebral blood flow to regions such as the thalamus and cortex [11, 12]. However, the most widely regarded theory involves the connections of the trigeminal (and by extension vagus) nerves with the Nucleus of the Solitary Tract (NTS). The NTS projects to brainstem nuclei such as the locus ceruleus and dorsal raphe nucleus that control neurotransmitters such as norepinephrine and serotonin. Increased norepinephrine release via repetitive stimulation from TNS is of particular interest given this neurotransmitter's known anticonvulsant effects [13]. Equally important to its efficacy, TNS is

associated with a relatively benign side effect profile. This includes headache in 4%, anxiety in 4%, and skin irritation in 14% [8, 14] although not currently FDA approved for use in the United States, TNS has received approval from related regulatory bodies in the European Union and Canada.

The neurostimulation device which has been FDA approved for longest period of time in DRE in children is VNS. This device was FDA approved for the treatment of medically refractory focal onset seizures in patient's age > 12 years in 1997. VNS was subsequently FDA approved for the adjunctive treatment of chronic and recurrent depression in 2005. Multiple studies in both adults and children have documented the efficacy of VNS for DRE. By repetitively stimulating the left vagus nerve, VNS has been shown to reduce seizures by at least 50% in 51-64% of implanted patients [15-18]. Increased seizure reduction is experienced by children with VNS regardless of seizure type (focal versus generalized onset) and history of prior unsuccessful surgeries such as lobectomies and callosotomies [19]. VNS is also efficacious in specific subpopulations of children with devastating epilepsy syndromes such as Lennox-Gastaut syndrome (LGS). This condition is marked by multiple types of debilitating seizures, developmental delay, and a slow spike and wave pattern on EEG. The seizures experienced by these children can include atonic (or drop attack) seizures, which are notoriously intractable to medications and have the potential to result in significant injury. VNS has been shown to significantly reduce such types of seizures [20], with comparable efficacy to more invasive procedures such as corpus callosotomy [21, 22]. Complications arising from VNS implantation are rare, including risks related to anesthesia, bleeding

from injury to the jugular vein, infection, and trauma to the vagus nerve (resulting in typically transient vocal cord paralysis). The most common side effects from VNS stimulation include hoarseness, cough (particularly following device parameter adjustments), paresthesias, and shortness of breath [23]. Unlike the (often worse) side effects that results from anti-seizure drugs, such side effects occur only during stimulation, generally diminish over time, and may be improved with simple adjustment of parameter settings [24].

Given their proven efficacy versus continue unsuccessful trials of anti-seizure drugs, it is imperative for physicians seeing children with DRE to consider treatment with neurostimulation. VNS, TNS, RNS, and DBS all have the potential to significantly reduce seizures, all without adding to the undesirable side effects of polypharmacy. Equally important, neurostimulation has the potential to ultimately reduce health care expenditures. This has already been proven with VNS, where implantation in those age 1-11 years has been associated with significantly reduced hospitalizations, emergency room visits, and average total healthcare costs [25]. This is also true for children age 12-17 years, where VNS implantation has been associated with significantly reduced hospitalizations, episodes of status epilepticus, and average total healthcare costs [25]. Given this, it is no wonder VNS is associated with significant improvements in Quality-Adjusted Life Years (QALY) in pediatric patients with DRE [25]. As healthcare providers, we owe it to our patients to act as their advocates and fight for the most efficacious treatment modalities available. If you practice is in a location where neurostimulation is not an option, I implore you to refer such children to a comprehensive epilepsy centers where such treatments can be offered.

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