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Delayed seizure control with responsive neurostimulation: patience is a virtue

To the Editor,

The efficacy of neurostimulation using vagus nerve stimulation (VNS), deep brain stimulation of the anterior nucleus of the thalamus, and responsive neurostimulation (RNS) has been shown to improve over time (Heck *et al*., 2014). RNS was recently approved by the United States Food and Drug Administration (USFDA) based on controlled trials that demonstrated safety and efficacy despite a third of patients failing epilepsy surgery and VNS (Heck *et al*., 2014). The USFDA approval employed a 12-week evaluation period. We report an adult with drug-resistant focal seizures who "failed" in the controlled clinical trial but ultimately achieved prolonged seizure freedom. We recommend that a minimum of a one-year period be maintained before considering neuromodulation to be a failure in scientific trials.

A 25-year-old right-handed woman developed focal seizures at 11 years of age. She became drug-resistant with monthly seizures despite multiple trials of antiseizure drugs singly and in combination in addition to VNS. Evaluation included normal 3 Tesla (T) high-resolution brain MRI with an epilepsy protocol. Scalp video-EEG monitoring demonstrated left anterior predominant hemispheric interictal epileptiform discharges. Seizures were both non-localized and left lateralized on ictal EEG. An ictal SPECT (late injection) demonstrated a decreased radiotracer uptake in the left temporal lobe. A magnetoencephalogram revealed no discrete cluster with the dipolar field widely distributed over the left frontal lobe. Intracranial EEG monitoring was pursued in an effort to localize a primary seizure onset zone using subdural strips and grid placement in the left frontal and temporal regions. Four seizures were recorded with seizure onset arising independently from both eloquent cortex in the left posterior frontal and the mesial frontal neocortex. Surgery was not pursued due to an anticipated postoperative deficit and two seizure onset zones.

She was subsequently enrolled in the RNS pivotal trial (Heck *et al*., 2014). She was seizure-free for the first month post-implantation. Initial parameters included a 2-mA current, 160-μsec pulse width, 200-Hz frequency, and burst duration of 100 msec. The estimated charge density with these parameters was 1 $\mu C/cm^2$. After the first month, seizures recurred, and additional reprogramming of her stimulation parameters was required. Her enrolment in the trial was terminated upon FDA approval, and her study status reflected that she was a "non-responder." At her 31-month visit, stimulation parameters had been modified to include intra-electrode bipolar stimulation and a lower frequency of 50 Hz with a charge density of 2 $\mu C/cm^2$. She is currently 83 months post-implantation and has remained clinically seizure-free for 52 months at these settings.

Our case illustrates the contrast between the result achieved in a short-term controlled clinical trial and the ultimate clinical response evident in long-term follow-up. Despite the "failure" identified in the initial "blinded" portion of the trial, our patient had a final outcome that resulted in prolonged seizure freedom. This highlights work from prior studies that showed that the median percent reduction in seizures after neuromodulation with RNS improved from 44% at one year to 53% at two years (Heck *et al*., 2014).

While the exact mechanism of improvement seen with neuromodulation is still unclear, potential mechanisms include changes in synaptic efficacy, long-term potentiation or depression, release of trophic factors, and potentially even neurogenesis (Heck *et al*., 2002). Our patient had minimal changes in her stimulation parameters yet became seizure-free. Optimal parameters are desirable for most forms of neurostimulation, however, they have yet to be defined (Heck *et al*., 2002). During the "open-label" period, her ASDs were not altered, and only minimal adjustments to her RNS were made. Therefore, we suspect that the effect of neuromodulation over time may have been greater than the changes made in the RNS parameters.

The results in the pivotal trial represented our patient as a non-responder despite the fact that she ultimately became seizure-free. This reflects a "failure" of the trial to address the impact of the tested device. Despite the potential for patients with drug-resistant focal seizures to remit each year, we believe the patient's seizure control was due to her neuromodulation (Callaghan *et al*., 2007). This suggests that perhaps re-evaluating trial designs of neuromodulation would be better represented by longer periods of "blinding" to capture patient populations such as ours. In the post-marketing experience, we can learn from single cases that add to our knowledge base of neurostimulation. Long-term analysis of patients may lead to improving outcome predictability by reproducing

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results of neurostimulation. Providing a "reasonable wait period" may lead to USFDA approval of devices that are beneficial to patients whose seizures are drug-resistant and who are not amenable to surgery.

The precise period of "wait time" remains unknown for all forms of neurostimulation. From a practical standpoint, while a longer follow-up period for evaluation is ideal, we recognize the difficulty in balancing the high cost of research, lower enrolment and high drop-out rate against an optimal time frame to identify a response to therapy. Similarly, most pharmaceutical regulatory trials are comprised of only several months and may not capture long-term effectiveness. Nevertheless, we recommend that a minimum of a one-year period be emphasized before considering RNS to be a "failure" from a clinical standpoint. This time frame is still likely to miss some "late responders," such as in the case of our patient. Nevertheless, it is a rough benchmark that is likely to capture the majority of responders and extend the effect beyond the period of the "sham" effect that may be seen in the first few months after implantation (Morris and Mueller, 1999; Morrell, 2011).

Despite "failure" in a controlled clinical trial, patients with RNS may ultimately respond to treatment. Reassessing the optimal duration in trial design for neurostimulation devices is necessary to include late responders. Doing so will allow for greater accuracy in providing more treatments to patients with drug-resistant epilepsy.

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TEST YOURSELF

(1) Is the FDA model for blinded studies adequately designed to predict responders to neuromodulation?

(2) In the RNS Pivotal trial, 9% of patients became seizure-free; is this number underestimating the actual number of patients who become seizure-free?

(3) Have studies identified the appropriate parameters for neuromodulation?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".