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Letter to the Editor

Vagus nerve stimulation versus "best drug therapy" in epilepsy patients who have failed best drug therapy

I would like to thank Dr. Hoppe and colleagues for their recent study published in *Seizure* examining vagus nerve stimulation (VNS) versus "best drug therapy" in medically refractory epilepsy patients.[1] However, I have concerns regarding the authors' methodology and conclusions. In this retrospective matched pairs case–control study, 20 intractable epilepsy patients who received VNS in addition to best medical therapy experienced no additional therapeutic benefit after >2 years compared to 20 individuals who received best medical therapy alone. Both groups were retrospectively selected from a significantly larger pool of patients found to be poor candidates for resective epilepsy surgery after having failed medical therapy. Thus, the essence of the question posed is: do patients who fail best drug therapy benefit more from further best drug therapy or from VNS? As both groups experienced clinical improvement in this study, with lower seizure frequency and improved psychological outcome, the authors imply VNS is no better than best medical therapy alone for medically refractory epilepsy. This sentiment is also reflected in Dr. Hoppe's recent editorial in *Seizure* provocatively entitled "Vagus nerve stimulation: Urgent need for the critical reappraisal of clinical effectiveness."[2] My concerns involve study design, equivalency of the two patient groups, inflated outcomes in the control group, and wider implications of over interpreting a spurious finding.

The authors argue that while nearly all previous VNS patient studies have shown a degree of *efficacy*, those investigations did not adequately examine therapeutic *effectiveness*, as they did not contain a control group. What is not clear, however, is why control patients in this study – those receiving best drug therapy alone – improved so dramatically during the period of observation. Does best medical therapy truly result in a >50% decrease in seizure frequency in >60% of patients who are already medically refractory? It is well documented that after failing 2 or more antiepileptic medications, intractable epilepsy patients are unfortunately unlikely to achieve seizure freedom with additional medication trials.[3,4] And while several new anti-seizure medications have become available since 1990,[5] these novel agents have had only a modest impact on the rate of intractable epilepsy.[6–8] One potential explanation for the apparent success of best drug therapy described by Hoppe et al. is that the patients were not already receiving "best drug therapy" before the study began. What is far more likely, however, is that the exceedingly favorable outcomes in the control group represent a spurious finding resulting from study design issues and inequivalent patient groups.

Among intractable epilepsy patients found to be poor candidates for resective surgery by Hoppe et al., 180 individuals received VNS while more than 500 patients received continued best drug therapy. Yet, only 40 of these >680 patients were selected for retrospective comparison. While the authors pursued this approach in hopes of creating two well-matched patient cohorts, it greatly under-samples available patient data, and in my opinion, does not achieve this goal. The authors report no statistical differences in terms of demographics and general characteristics between these two patient groups, but this is inherently expected, as the groups were modeled as such. But the most important difference between the two patients groups is that *something* ultimately led to the physician–patient decision to pursue VNS in one group, but not the other. Furthermore, the authors report that patients who received VNS had significantly greater seizure severity and frequency than those in the best drug therapy group. This is a critical confounder that may have influenced the decision to pursue VNS. There were likely other reasons for choosing VNS in some patients but not others that are unknowable retrospectively, yet may be of importance. Finally, what defines the beginning of the study is easily discernible for VNS-implanted patients, but for control patients represents an arbitrary point on a continuum of ongoing "best drug therapy." These problems make data interpretation difficult.

Another concern I have involves the wider potential implication of erroneously inflating the efficacy of "best drug therapy" in medically refractory epilepsy patients. If dramatic clinical improvement can be expected in >60% of intractable epilepsy patients with continued best drug therapy alone, why consider resective epilepsy surgery? Resection is a potentially curative treatment option in some focal epilepsy patients, though certainly not without risk. But hesitating based solely on the data presented by Hoppe et al. would be a mistake. Intractable seizures are associated with cognitive and neuropsychological impairment, diminished quality of life, and increased risk of death.[9] In localizable epilepsy, early surgical evaluation is supported by class I evidence and national guidelines.[10–12] Given the current underutilization of resective epilepsy surgery,[4,13] the accuracy of treatment success rates used to make decisions in epilepsy treatments is of utmost importance.

Based on their data interpretation, Hoppe et al. imply that VNS does not have clinical effectiveness beyond medical therapy. VNS is not without problems, as properly delineated by Hoppe et al., including treatment failure, surgical complications, device-site infection, incompatibility with MRI, and others. Therefore, if it is truly not effective, it should not be used, and the 100,000 implants performed thus far may be thrown into question. Indeed, VNS is not a replacement for resective epilepsy surgery, as nearly half of patients do not receive worthy clinical benefit from VNS, and complete seizure-freedom is rare.[14] Nevertheless, numerous studies have consistently demonstrated that seizure frequency is diminished greater than 50% in half or more of patients treated with VNS.[15] In appropriate patients with disabling seizures who are not favorable candidates for resection, this real chance for improvement makes VNS a reasonable treatment option to consider.

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In the end, the ultimate test of a treatment's clinical effectiveness is not a retrospective cohort study, or a systematic review, or the experience of a biased provider. It is a blinded, randomized-controlled trial. Three such trials have examined VNS, demonstrating significant clinical improvement with treatment when compared to sham stimulation.[16–18] I do applaud the continued scientific skepticism and worthy pursuit of Hoppe et al., as further exploration of the clinical effectiveness of VNS and alternative epilepsy treatments is needed. However, once a specific question has been addressed by a randomized-controlled trial, as in this case, a serious challenge to it should be based in another such trial.

Conflict of interest statement

The author has no conflicts of interest to disclose and has no affiliation with Cyberonics, Inc., the manufacturer of VNS Therapy.

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