

## BRAIN STIMULATION FOR EPILEPSY: STIMULATING RESULTS?

### Long-Term Follow-Up of Patients with Thalamic Deep Brain Stimulation for Epilepsy

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The authors describe long-term follow-up (mean, 5 years) in patients with anterior (AN) ( $n = 6$ ) or centromedian ( $n = 2$ ) thalamic deep brain stimulation (DBS) for epilepsy. Five patients (all AN) had 50% seizure reduction, although benefit was delayed in two until years 5 to 6, after changes in

antiepileptic drugs. DBS electrode implantation in AN patients was followed by seizure reduction 1 to 3 months before active stimulation, raising the possibility of a beneficial microthalamotomy effect.

### Hippocampal Electrical Stimulation in Mesial Temporal Lobe Epilepsy

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**BACKGROUND:** Adjustable, reversible therapies are needed for patients with pharmacoresistant epilepsy. Electrical stimulation of the hippocampus has been proposed as a possible treatment for mesial temporal lobe epilepsy (MTLE).

**METHODS:** Four patients with refractory MTLE whose risk to memory contraindicated temporal lobe resection underwent implantation of a chronic stimulating depth electrode along the axis of the left hippocampus. The authors used continuous, subthreshold electrical stimulation (90  $\mu$ sec, 190 Hz) and a double blind, multiple cross-over, randomized controlled design, consisting of three treatment pairs, each containing two 1-month treatment periods. During each treatment pair the stimulator was randomly turned ON 1 month and OFF 1 month. Outcomes were assessed at monthly intervals in a double blind manner, using standardized instruments and accounting for a washout period.

The authors compared outcomes between ON, OFF, and baseline periods.

**RESULTS:** Hippocampal stimulation produced a median reduction in seizures of 15%. All but one patient's seizures improved; however, the results did not reach significance. Effects seemed to carry over into the OFF period, and an implantation effect cannot be ruled out. The authors found no significant differences in other outcomes. There were no adverse effects. One patient has been treated for 4 years and continues to experience substantial long-term seizure improvement.

**CONCLUSION:** The authors demonstrate important beneficial trends, some long-term benefits, and absence of adverse effects of hippocampal electrical stimulation in mesial temporal lobe epilepsy. However, the effect sizes observed were smaller than those reported in non-randomized, unblinded studies.

### COMMENTARY

When a patient's partial seizures fail to come under control with medication, resection of the seizure focus offers the best hope for complete seizure control. Unfortunately, a significant fraction of patients with poorly controlled epilepsy are not candidates for resection of the seizure focus because their seizures arise from multiple sites or from sites that cannot

be removed safely. Indirect brain activation using vagus nerve stimulation has provided palliation for this group of patients. Unfortunately, the seizure relief provided often is minimal (1).

Alternative, nonresective approaches to treating epileptogenic foci have been proposed in hope of lessening the seizure burden without causing the neurological deficits anticipated with resection in this group of patients. Multiple subpial transections remain a viable option for treating a well-localized seizure focus in functional tissue. Although the effect of this disconnection technique in isolation is difficult to assess (given that it often is used in combination with resection), it seems clear that multiple subpial transections can sometimes dramatically

reduce or eliminate seizures (2). Gamma knife radiotherapy trials have demonstrated that focused radiation can be used effectively to treat a well-circumscribed seizure focus, such as the hippocampus (3) or the hypothalamus (4). It remains to be seen whether gamma knife radiotherapy will be effective in treating more diffuse seizure foci and whether it will preserve function in the region treated.

Perhaps, even more attractive are approaches expected to have a “temporary” effect on tissue, such as electrical stimulation, focal cooling (5), or focal medication delivery (6). The effect of these techniques might be assessed and reversed by stopping treatment if the negative consequences outweigh the improved seizure control. Alternately, the negative effects might be accepted but limited to the times when seizures otherwise are inevitable, as assessed by a computerized seizure detection paradigm. Focal cooling of the seizure focus (5) and localized delivery of medication (6) have been proposed as options, but these techniques have not progressed to use in human trials. In contrast, direct electrical stimulation of the brain has advanced to the point where investigators are now enrolling patients in two large, multicenter, randomized, controlled studies to assess the safety and efficacy of anterior thalamic and cortical stimulation (7,8).

The brief reports from Tellez-Zenteno and colleagues and Andrade et al. may offer us a preview of what might come from the more definitive, multicenter trials. Given the very small number of patients in their series, any claims for demonstration of safety must be taken as preliminary. Nevertheless, small numbers of patients might be helpful in assessing the potential for efficacy (at least for prominent improvements in seizure control), as the natural history of seizure control in this group of patients has been established.

Although the finding by Andrade and colleagues that the benefit from anterior thalamic stimulation appears to persist for years is somewhat encouraging, their report raises some important concerns. Most significant was their finding that stimulation added very little to the effect on seizure control from what was already noted shortly after electrode implantation (i.e., before stimulation started). As they indicated, the improved seizure control may have been related to a favorable effect of placing a small lesion in the thalamus or, alternatively, a placebo effect. While the patients did not have prominent seizure reduction from the stimulation, neither did they have negative consequences associated with the procedure, which is in keeping with other small trials of thalamic stimulation. This finding is expected, given that the technique has a well-established safety record as a treatment for other neurological disorders.

The relatively modest effect of anterior thalamic stimulation observed in the Andrade et al. series is not without precedent. The same investigators previously reported similar results in a subset of these patients with less extensive follow-up.

Kerrigan et al. found that 4 of 5 patients receiving open-label anterior thalamic stimulation had a reduction in severity of seizures, although only one had a reduction in total seizure frequency (9). This outcome led them to speculate that thalamic stimulation might be better at preventing seizure propagation than seizure initiation.

Tellez-Zenteno and colleagues report encouraging results with patients undergoing chronic stimulation of well-defined, unilateral medial temporal seizure foci. The n-of-1 crossover trial design is important in that it markedly reduces the potential for a placebo effect. It also increases the power of the small series to demonstrate a fairly modest benefit. Perhaps because of the design, the results, though clearly positive, are considerably less favorable than those reported from uncontrolled studies (10,11). As the authors note, this effect has typically been found with stimulation trials in epilepsy: randomized, controlled trials demonstrate that the impressions from open-label studies are far too optimistic. Similar to the pilot thalamic stimulation trials, this study was notable for an absence of adverse consequences of stimulation.

In contrast to thalamic stimulation, chronic cortical stimulation is not used routinely to treat other neurological disorders. Thus, published and ongoing cortical stimulation studies are providing novel safety information. To date, evaluation following acute cortical stimulation has shown no stimulation-related pathological changes (10,12). Seizure exacerbations do not seem to be more common than might otherwise be expected in patients with severe, refractory epilepsy. However, accrual of additional safety data will be especially important in the current cortical stimulation study, since the accumulated experience with this technique is much less than with thalamic stimulation. For either type of stimulation, the magnitude of response in patients enrolled in the ongoing multicenter trials will be critical to determining how these techniques might be used in clinical practice.

by Paul Garcia, MD

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