

# OUTCOMES REMAIN AMBIVALENT FOR DEEP BRAIN STIMULATION AND EPILEPSY

**Deep Brain Stimulation in Patients with Refractory Temporal Lobe Epilepsy.** Boon P, Vonck K, De Herdt V, Van Dycke A, Goethals M, Goossens L, Van Zandijcke M, De Smedt T, Dewaele I, Achten R, Wadman W, Dewaele F, Caemaert J, Van Roost D. *Epilepsia* 2007;48(8):1551–1560. **PURPOSE:** This pilot study prospectively evaluated the efficacy of long-term deep brain stimulation (DBS) in medial temporal lobe (MTL) structures in patients with MTL epilepsy. **METHODS:** Twelve consecutive patients with refractory MTL epilepsy were included in this study. The protocol included invasive video-EEG monitoring for ictal-onset localization and evaluation for subsequent stimulation of the ictal-onset zone. Side effects and changes in seizure frequency were carefully monitored. **RESULTS:** Ten of 12 patients underwent long-term MTL DBS. Two of 12 patients underwent selective amygdalohippocampectomy. After mean follow-up of 31 months (range, 12–52 months), one of 10 stimulated patients are seizure-free (>1 year), one of 10 patients had a >90% reduction in seizure frequency; five of 10 patients had a seizure-frequency reduction of  $\geq 50\%$ ; two of 10 patients had a seizure-frequency reduction of 30–49%; and one of 10 patients was a nonresponder. None of the patients reported side effects. In one patient, MRI showed asymptomatic intracranial hemorrhages along the trajectory of the DBS electrodes. None of the patients showed changes in clinical neurological testing. Patients who underwent selective amygdalohippocampectomy are seizure-free (>1 year), AEDs are unchanged, and no side effects have occurred. **CONCLUSIONS:** This open pilot study demonstrates the potential efficacy of long-term DBS in MTL structures that should now be further confirmed by multicenter randomized controlled trials.

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## COMMENTARY

**N**eurostimulation is a technique used in many areas of neurology. Based on adequate clinical trials, deep brain

stimulation (DBS) is an accepted and proven technique for disorders such as tremor, movement disorder, and even pain (1). DBS also has been evaluated for epilepsy but still is not accepted as a routine treatment modality. The most salient reasons for the infrequent use of DBS for patients with epilepsy are because there is no consensus regarding the location of optimal stimulation sites and for which specific seizure types it is most effective. Current, ongoing studies, which have not yet been reported in full, involve the seizure focus and the thalamus (2–4). Even within the thalamus, it is not clear whether the centromedial nucleus or the anterior nucleus is the best site for DBS. There is some evidence that DBS for epilepsy also may be effective at the subthalamic nucleus, the caudate nucleus, and the cerebellum (2). The cerebellum actually was the first site to undergo DBS experimentation, but so far the results of small studies are not encouraging (5) and many trials were designed with so few patients that no reliable conclusions can be made (6).

In the Boon et al. study, stimulation was given intermittently over 24 hours, irrespective of seizure activity at the seizure site. In other words, a vagus nerve stimulation-like paradigm was employed, but the stimulation was applied locally instead of from a distant site. The patients participating in the study had mesial temporal lobe foci and were undergoing epilepsy surgery evaluation. All the patients had been implanted with electrodes for the surgical evaluation, so they were ethically appropriate subjects to recruit for an efficacy study of this methodology. Furthermore, patients were made aware of the fact that DBS was being administered.

Three patients, who had previously been reported on, served as the rationale for further evaluating the technique, as they all had done well with focal DBS (7). Backed by the initial success, the authors intended to implant 12 additional patients with stimulating electrodes. The inclusion criteria for these patients were: 1) suspicion of a mesial temporal focus on the basis of video-EEG monitoring, 2) at least one complex partial seizure monthly in spite of taking at least two antiepileptic drugs (AEDs), and 3) incongruent findings among other evaluations to localize the seizure focus, requiring invasive video-EEG monitoring in the bilateral medial temporal lobes and other subdural areas. In addition to the other electrode grids that were required for surgical evaluation, two quadrupolar electrodes for DBS were placed in each hemisphere through two parietooccipital burrholes—one in the amygdala and one in the anterior part of the hippocampus. All electrode grids and DBS electrodes were implanted during the same surgery.

After 48 hours of video-EEG monitoring, the AEDs were downtitrated until the patient's habitual seizures appeared. If there was evidence of a focal or regional or bilateral mesial temporal ictus, then the patient was offered a trial of continuous DBS; all 12 patients initially consented to be in the study. If only one temporal lobe had an ictal focus, then the patients

were offered unilateral DBS. If both temporal lobes had ictal foci, then bilateral DBS was offered. If spikes on the EEG were reduced by 50% after stimulation for 7 days with an external stimulator, compared with the condition during video EEG with AED taper, then the external DBS generator was permanently implanted in the abdominal area. If there was not a 50% reduction in spikes after a week of stimulation, the external stimulation was continued for another 21 days. If the number of spikes were still not reduced by >50%, then another 3 weeks of acute stimulation was allowed, with adjusted stimulation frequency. At that point, if a >50% spike reduction was still not achieved, then the patient was offered resective surgery or a continuation of the AED treatment. There were 2 patients among the 12 who went on to have epilepsy surgery; they both subsequently became seizure-free. One of the two patients had a right-sided focal ictal onset and went immediately into surgery, without ever trying DBS. The other patient attempted DBS, but the ictal spikes were not reduced by 50% after 6 weeks of treatment. The other 10 patients had a generator implanted, as they fulfilled the criteria for chronic implantation.

The results for the patients given DBS are mediocre, with only one who became seizure-free and one who had a 90% seizure reduction. The level of seizure reduction overall was very similar to that seen in vagus nerve stimulation trials or when adding an experimental AED. Side effects were few and minor, except one patient who was administered DBS and had asymptomatic hemorrhagic bleeding.

Unfortunately, the lack of a placebo group affects the reliability of the study's outcomes, and a run-in placebo period would have been helpful to cull out placebo responders. Even the major criterion for stimulation—spike reduction by over 50%—is a totally unproven method for selecting responders and would have benefited from a placebo run-in. For patients with an inoperable epileptic focus, DBS might be an alternative. Yet, if vagus nerve stimulation produces efficacy similar to DBS, why should invasive implantation of electrodes in the brain be performed, when the same result using peripheral stimulation might suffice? However, considering the increasing number of applications of DBS for neurological diseases, it may be important to continue exploring DBS for epilepsy treatment but with more solid study design.

by Elinor Ben-Menachem, MD, PhD

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