

# Treatment of Medically Refractory Essential Tremor

Elan D. Louis, M.D

Essential tremor is among the most prevalent neurologic diseases, estimated to affect approximately 7 million persons in the United States alone.<sup>1</sup> The primary feature is kinetic tremor, affecting the hands and arms, although tremor may take on other forms (i.e., postural, intentional, and rest tremors), may affect other body regions (i.e., head and voice), and may be accompanied by additional motor features (e.g., gait ataxia) and nonmotor features. Emerging evidence suggests that the disease may be neurodegenerative.<sup>2,3</sup> As with other such diseases, effective pharmacotherapies for essential tremor have been elusive. There are few available medications, with the mainstays of therapy being beta-blockers (especially propranolol), the antiepileptic drug primidone, and several medications that enhance  $\gamma$ -aminobutyric acid neurotransmission, but their efficacy is limited. Hence, a large number of patients have medically refractory disease and do not receive adequate treatment.<sup>4,5</sup> One approach to the treatment of these patients is surgical, with deep-brain stimulation being the most common surgical treatment.<sup>6</sup> Deep-brain stimulation is generally preferable to previously used lesioning procedures (i.e., thalamotomy) because it can be reversed by removing the electrodes, it leaves little or no residual damage, and it is adjustable with the use of a programmable stimulator. Nevertheless, deep-brain stimulation is associated with risks, which include intracranial bleeding and infection, as well as malpositioned electrodes, the need to replace the battery periodically, and hardware issues such as lead breakage.

Elias and coauthors now report in the *Journal* the results of a double-blind, randomized, sham-controlled trial of magnetic resonance imaging (MRI)-guided focused ultrasound to create a unilateral thalamic ablation for the treatment of essential tremor.<sup>7</sup> The patients in their study were enrolled at eight international centers. Scores for hand tremor improved significantly more after focused ultrasound thalamotomy than after the sham procedure, as did measures of disability and quality of life. The results are promising, particularly since this procedure,

unlike traditional thalamotomy, does not require entering the cranium with a probe.

Nevertheless, there are several important concerns about this study. The first is the limited follow-up period, which was 12 months. The sustained benefit at 2 years, 3 years, and 5 or more years is not known. Studies with longer follow-up intervals are needed to address this issue. This is particularly important because of tachyphylaxis, which is the second concern. The primary outcome measure was the score for hand tremor (on a scale ranging from 0 to 32, with higher scores indicating more severe tremor) at 3 months. As shown in Table S1 in the Supplementary Appendix (available with the full text of the article by Elias et al. at NEJM.org), the tremor score in the group that underwent focused ultrasound thalamotomy increased from 8.84 (at 1 month) to 9.55 (at 3 months) to 10.13 (at 6 months) to 10.89 (at 12 months). The increase from months 1 to 12 was 23%. Secondary outcome measures showed similar or greater increases during the 12-month follow-up period (e.g., the Clinical Rating Scale for Tremor score increased from 23.38 at 1 month to 32.38 at 12 months, which is a 38% increase). Whether this loss of efficacy, which is also seen to some extent with deep-brain stimulation, is due to disease progression or tolerance is not clear,<sup>8</sup> although typical estimates of the rate of disease progression in essential tremor make the former possibility less likely.<sup>9</sup> Third, as one can see from the graphs of individual-level responses (Fig. 1B in the article by Elias et al.), the procedure did not achieve large improvements in everyone; the percentage change in tremor was less than 20% in 9 of 56 patients.

Aside from the concerns discussed above, there are several important caveats. The first is that the procedure is a thalamotomy. Hence, it creates a fixed brain lesion. With deep-brain stimulation, there is the potential to adjust stimulator settings in order to obtain further therapeutic gains, but there is no such potential with thalamotomy. Second, the procedure is not suitable for all patients; in particular, skull thickness presents a problem in some cases. As noted

by the authors, “Transcranial delivery of focused ultrasound was difficult to achieve in five of the study patients, probably because of the frequency and other properties of the acoustic wave, as well as individual cranial characteristics.”<sup>7</sup> Third, the most common side effect involved altered sensation, and this deficit remained permanent in 14% of patients.

Even with these concerns and caveats, pros and cons, the procedure will take its place among other surgical procedures for medically refractory essential tremor. Given the perception that it is less invasive than other approaches because it does not involve burr holes and intracerebral electrodes, as well as the evidence that patients with essential tremor are perhaps particularly harm avoidant,<sup>10</sup> the procedure may allow more patients to avail themselves of a surgical option for the treatment of this often disabling disease. A head-to-head comparison with deep-brain stimulation would facilitate the direct comparison of the two approaches.

Disclosure forms provided by the author are available with the full text of this article at [NEJM.org](http://NEJM.org).

From the Department of Neurology and the Center for Neuroepidemiology and Clinical Neurological Research, Yale School of Medicine, and the Department of Chronic Disease Epidemiology, Yale School of Public Health, Yale University, New Haven, CT.

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