

## EDITORIALS



## Parkinson's Disease — What's the FUS?

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Parkinson's disease causes progressive motor and cognitive dysfunction. Medications aim to replace deficient dopamine in the brain and reduce the characteristic slowness, stiffness, and tremor. However, as the disorder progresses, medications provide shorter duration of benefit and produce involuntary dyskinetic movements. Surgical approaches to Parkinson's disease that can provide additional benefit at these later stages include deep-brain stimulation and ablative lesions in the nuclei of the basal ganglia.<sup>1,2</sup> These procedures are considered to produce clinical benefit by modulation of pathologic oscillatory signals.<sup>3</sup>

Deep-brain stimulation for the treatment of Parkinson's disease has predominantly targeted the subthalamic nucleus or the internal segment of the globus pallidus. Clinical trials, including two that were previously reported in the *Journal*,<sup>1,4</sup> have shown the efficacy and safety of deep-brain stimulation of the left and right subthalamic nuclei, with a reduction in the severity of motor signs of 40 to 60% and a reduction in medication use of up to 50%. Deep-brain stimulation involves a small craniotomy with implantation of stimulating electrodes connected to a pulse generator that is usually implanted in the chest and that requires replacement every 2 to 25 years, depending on the device.<sup>4,5</sup> By modifying the frequency and amplitude of the electrical stimulus, it is possible to improve motor symptoms of parkinsonism and minimize untoward effects of deep-brain stimulation on an individualized basis as the disease progresses. The implantation of electrodes has a 1 to 5% risk of major adverse events such as hemorrhage, stroke, or infection.<sup>6</sup> Less severe complications include dystonia, dysarthria, gait impairment, dyskinesia, swallowing

dysfunction, or change in verbal fluency; however, modification of the device programming may alleviate these effects. Nevertheless, some patients are wary of the implantation surgery and hardware and therefore decline to undergo deep-brain stimulation.

Alternative strategies that produce fixed brain lesions, such as radiofrequency ablation and focused ultrasound (FUS), can also target the subthalamic nucleus. Radiofrequency ablation of the subthalamic nuclei in both hemispheres reduces the symptoms of parkinsonism to a similar degree as deep-brain stimulation in both hemispheres, at least initially, and radiofrequency ablation in one hemisphere can be used to improve symptoms on the opposite side of the body when tremor is severe on just one side. The benefit of radiofrequency subthalamotomy persists up to 3 years and may then diminish — a situation that reflects the worsening of Parkinson's disease or the return of abnormal activity in the subthalamic nucleus.<sup>7,8</sup> Like deep-brain stimulation, radiofrequency ablation requires craniotomy; it also has similar risks of hemorrhage and stroke. Its advantages include an absence of implanted devices and no requirement for subsequent programming of the pulse generator; however, the inability to modulate activity in the subthalamic nucleus is also its limitation. There are also potentially irreversible adverse events, such as moderate-to-severe dyskinesia or hemiballismus, gait impairment, dysarthria, and impaired verbal fluency.

More recently, focused ultrasound has been approved for the treatment of intractable essential tremor by producing lesions in the ventral intermediate nucleus of the thalamus.<sup>9</sup> Ablation

with focused ultrasound has the advantage of producing lesions without the need for craniotomy. Yet, focused ultrasound thalamotomy for tremor has not yet been shown to be safer than ablation methods that require craniotomy. Nevertheless, patients who are unwilling or unable to undergo craniotomy may be candidates for focused ultrasound ablation.

This issue of the *Journal* includes a report of a randomized clinical trial of focused ultrasound in one hemisphere in 40 participants with markedly asymmetric Parkinson's disease and prominent tremor who were considered to be poor candidates for deep-brain stimulation or declined to undergo the procedure.<sup>10</sup> A focused ultrasound-produced lesion in one hemisphere reduced the motor features of parkinsonism on the opposite side of the body by 50%, as compared with essentially no improvement in a group of patients who underwent a sham procedure. However, in this small trial, the group of patients who underwent focused ultrasound had almost 5 times as many adverse events as those who underwent the sham procedure. Most adverse events in the active-treatment group were transient, but they included dysarthria in 15 of 27 patients, which persisted in 1 patient at 12 months; weakness in 5 patients, which persisted as clumsiness or asymmetric stride in 2 patients at 12 months; and gait unsteadiness in 13 patients, which persisted in 1 patient at 12 months. These adverse events in a group of relatively young patients and the lack of ability to modulate treatment over time to treat prominent tremor raise questions about the appropriate implementation of focused ultrasound-produced lesions for the treatment of Parkinson's disease.

What tests should a new surgical treatment for Parkinson's disease pass before routine clinical adoption? A minimum standard would include safety and efficacy as compared with currently available approaches and the identification of the population of patients for whom the procedure is most appropriate. Focused ultrasound-produced lesions provide an option for patients who decline to receive electrode implantation or who do not have access to the resources necessary for regular reprogramming of a deep-brain stimulation device. Furthermore, like radiofrequency ablation, an ultrasound-produced lesion results in a hole in the brain that cannot be reversed. The accuracy and size of lesion place-

ment may improve with experience, but current ultrasound-targeting methods cause at least transient, and occasionally long-lasting, weakness and speech difficulties. Side effects such as dysarthria may limit application to focused ultrasound-produced lesions in one hemisphere because the frequency of dysarthria is likely to be greater with procedures that are conducted in both hemispheres. Currently, coexisting conditions such as dementia are contraindications to deep-brain stimulation because they enhance the risk of cognitive and psychiatric adverse effects. Would focused ultrasound-produced lesions be an option in such patients or in those without access to the resources necessary for ongoing programming? In this trial, most of the patients would have been eligible for deep-brain stimulation but had declined to undergo that procedure; in our estimation, only three patients had a contraindication to deep-brain stimulation that was due to coexisting conditions.

The development of alternative procedures to deep-brain stimulation is important to the field of Parkinson's disease treatment. The current trial begins the path to that goal, and improvements in targeting may improve the risk-benefit ratio and permit the use of lesions in both hemispheres, which would widen the population of eligible patients. Limiting the treatment to one side of the brain by ultrasound-produced lesioning constrains the application, since most patients with Parkinson's disease have progression of symptoms on both sides of the body, as was shown in a trial of radiofrequency subthalamotomy in one hemisphere.<sup>7</sup> The potential advantages and limitations of focused ultrasound-produced lesioning should be discussed with patients. We hope that improved technique will reduce the associated risks and increase the applicability of this provocative procedure.

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

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## Antenatal Glucocorticoids in Low-Resource Settings — Who, When, and Where?

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It has been known for decades that women who receive betamethasone or dexamethasone before preterm delivery have neonates who fare better than those of women who do not receive these agents. The earliest established effect of this glucocorticoid therapy was an acceleration in fetal lung maturation, with a marked decrease in the incidence of neonatal respiratory distress syndrome. Over time, additional benefits became evident, including decreased risks of intraventricular hemorrhage, necrotizing enterocolitis, early neonatal infection, and death.<sup>1</sup> Most evidence supporting the use of antenatal glucocorticoids comes from high-resource countries, where the neonatal benefits are accompanied by minimal risks to the mother or child. Antenatal glucocorticoids have thus become the standard of care for preterm births in high-resource settings.<sup>2,3</sup>

Antenatal glucocorticoids are inexpensive and easily administered by intramuscular injection. As such, they would appear to be an ideal redress for the staggering toll of prematurity in low- and middle-income countries, where each year more than 1 million preterm infants die in the first year of life and countless more face lifelong disability.<sup>4</sup> However, major questions were raised about the more global use of this therapy after the results of the Antenatal Corticosteroids Trial (ACT) were published in 2015.<sup>5</sup> The investigators of ACT, which was conducted in sub-Saharan Africa, South Asia, and Latin America, used a pragmatic, cluster-randomized

design to assess whether antenatal dexamethasone could be safely and effectively administered in community and primary care settings where access to obstetricians and neonatal intensive care was limited. The results were troubling: not only did the intervention fail to reduce mortality among neonates with a birth weight below a site-specific fifth percentile (the trial proxy for prematurity), but it was also associated with a higher overall neonatal mortality than placebo (27.4, vs. 23.9 deaths per 1000 live births) and a higher incidence of suspected maternal infection (3%, vs. 2%). These findings prompted policymakers to urge caution in the use of antenatal glucocorticoids in low-resource settings and to call for further research.<sup>6</sup>

The results of the World Health Organization (WHO) Antenatal Corticosteroids for Improving Outcomes in Preterm Newborns (WHO ACTION-I) trial, now reported in the *Journal*,<sup>7</sup> are an answer to that call. In this trial, which was conducted in hospitals in five low-resource countries, almost 3000 women between 26 weeks 0 days and 33 weeks 6 days of gestation who were at imminent risk for delivery were randomly assigned to receive dexamethasone (up to four intramuscular injections of 6 mg, administered 12 hours apart) or matching placebo. Neonatal death occurred less frequently in the dexamethasone group than in the placebo group (in 19.6% vs. 23.5%; relative risk, 0.84; 95% confidence interval [CI], 0.72 to 0.97), as did the combined outcome of stillbirth or neonatal death (in 25.7%