Deep-Brain Stimulation for Parkinson’s Disease

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A 72-year-old right-handed man with a 12-year history of Parkinson’s disease presents with a diminished response to medication and right-sided dyskinesia (involuntary movements). During the past several years, he has been taking multiple drugs for Parkinson’s disease, including a monoamine oxidase inhibitor, amantadine, a dopamine agonist, and carbidopa–levodopa. He reports that with his current regimen, which includes 1.5 tablets of 25/100 carbidopa–levodopa taken every 2 hours, he has marked reductions in tremor, rigidity, and bradykinesia and substantial improvement in his walking. Despite multiple interval and dose adjustments, however, he also reports 6 hours per day of “off” time, when his symptoms are unresponsive to his current medication regimen. In addition, he has severe, disabling right-sided dyskinesia 4 hours per day. Symptoms affecting his left side are mild and not bothersome. His cognition is excellent, his neurologic examination is otherwise normal, and he has no other coexisting medical conditions. His neurologist refers him to a neurosurgeon for consideration of deep-brain stimulation.

The Clinical Problem

Parkinson’s disease typically develops between the ages of 55 and 65 years and occurs in 1 to 2% of persons over the age of 60 years. Approximately 0.3% of the general population is affected, and the prevalence is higher among men than women, with a ratio of 1.6 to 1.0. Motor manifestations of the disorder commonly include a resting tremor, a soft voice, small handwriting (micrographia), stiffness (rigidity), slowness of movements (bradykinesia), shuffling steps, and difficulties with balance. A classic symptom is resting tremor, although 20% of patients do not have it. Parkinson’s disease also has a multitude of nonmotor manifestations, including disturbances of mood (e.g., depression, anxiety, and apathy), cognition (e.g., frontal-lobe dysfunction, memory difficulties, and dementia), and sleep (e.g., apnea and sleep disorders), as well as autonomic dysfunction (e.g., sexual dysfunction, digestive problems, and orthostasis).

One third of patients with Parkinson’s disease lose employment within a year after diagnosis, and within 5 years, a majority are not employed full time. Estimated costs of drug treatment range from $1,000 to $6,000 per patient per year. The annual health care cost per patient ranges from $2,000 to more than $20,000 per year. The risk of death from any cause is nearly doubled for patients with Parkinson’s disease, regardless of the duration of the disease. Referral to a neu-
rologist has recently been reported to be associated with decreases in morbidity, mortality, and nursing home placement.\textsuperscript{12}

**PATHOPHYSIOLOGY AND EFFECT OF THERAPY**

Parkinson’s disease is a neurodegenerative syndrome involving multiple motor and nonmotor neural circuits in the basal ganglia.\textsuperscript{3,13,14} Human and animal physiological recordings have shed light on many of the complex brain-signaling disturbances that underpin Parkinson’s disease.\textsuperscript{14,15} Dysfunction in motor and nonmotor thalamocortical loops in the parallel and segregated basal ganglia results in characteristic changes in rates of neuronal firing, firing patterns, and oscillatory brain-cell activity.\textsuperscript{13,15}

Typically, patients with Parkinson’s disease have a robust response to one or more medications. However, after 5 years of therapy, medication-related complications develop in a majority of patients. Such complications include dyskinesia and “on–off” fluctuations, in which a sudden, sometimes unpredictable loss of benefit from medication occurs, characterized by reduced mobility, tremor, rigidity, and other motor and nonmotor manifestations.\textsuperscript{2,16} Some symptoms (e.g., difficulties with gait, balance, speech, swallowing, or cognition) may become progressively resistant to carbidopa–levodopa and other pharmacologic therapies. Patients with symptoms that are responsive to levodopa and selected other symptoms are appropriate potential candidates for deep-brain stimulation.\textsuperscript{17}

Deep-brain stimulation is a surgical technique in which one or more electrodes attached to leads are implanted in specific regions of the brain (Fig. 1). The electrodes are connected to a device called an impulse generator, which delivers electrical stimuli to brain tissue in order to modulate or disrupt patterns of neural signaling within a targeted region. Two specific sites in the brain have been most commonly targeted for deep-brain stimulation in Parkinson's disease: the subthalamic nucleus and the internal segment of the globus pallidus. Both are nuclei in the basal ganglia, where much of the degenerative change in Parkinson's disease occurs.

Deep-brain stimulation acts on the cells and fibers located closest to the implanted electrode, in most cases inhibiting cells and exciting fibers\textsuperscript{18,19} (Fig. 2). The therapy influences multiple thalamocortical circuits, downstream pathways, and other brain structures. Deep-brain stimulation changes the firing rate and pattern of individual neurons in the basal ganglia.\textsuperscript{20} The electrical current also acts at synapses and triggers neighboring astrocytes to release a wave of calcium and to promote local release of neurotransmitters (e.g., adenosine and glutamate).\textsuperscript{21-23} Finally, the therapy increased blood flow and stimulates neurogenesis.\textsuperscript{24} All these effects occur cumulatively across a large neural network, extending beyond local neuronal cell bodies and axons located around the electrical field (Fig. 3). Thus, deep-brain stimulation has electrical, chemical, and other neural-network influences on brain tissue. However, it remains unclear exactly how these influences lead to changes in the symptoms of Parkinson’s disease; therefore, the benefits of this mode of therapy have been established more or less empirically.

**CLINICAL EVIDENCE**

Four randomized, controlled clinical trials of deep-brain stimulation have been performed. Three have made comparisons with medical therapy, and one compared deep-brain stimulation with a no-stimulation group.\textsuperscript{25-28} The end points of these trials included quality of life, as measured by the Parkinson's Disease Questionnaire (PDQ-39; scores range from 0 to 100, with higher scores indicating worse function)\textsuperscript{29}; the severity of motor symptoms while the patient was not taking medication, as assessed with the Unified Parkinson's Disease Rating Scale (UPDRS-III; scores range from 0 to 108, with higher scores indicating poorer condition)\textsuperscript{30}; and the number of hours per day spent in the “on” state without dyskinesia, as assessed by means of a dyskinesia diary.\textsuperscript{31}

In the first of these trials, which was conducted in Germany and Austria, 156 patients with Parkinson’s disease and persistent motor symptoms despite optimal medical therapy\textsuperscript{25} were randomly assigned to undergo bilateral deep-brain stimulation of the subthalamic nucleus or to receive medical therapy. At 6 months, patients assigned to deep-brain stimulation had significantly better mean scores on the PDQ-39 (31.8 vs. 40.2) and the UPDRS-III (28.3 vs. 46.0).
The three subsequent trials were similar to the first in design, though with some differences in specific features and in the choice of primary outcome measures. In a trial involving 255 patients in the United States, with 6 months of follow-up, patients who underwent deep-brain stimulation of the subthalamic nucleus or globus pallidus interna gained a mean of 4.6 hours per day of “on” time, versus 0 hours per day for the medical-therapy group. In a trial involving 366 patients in the United Kingdom, at 1 year, the mean PDQ-39 score was 32.5 among patients undergoing subthalamic deep-brain stimulation versus 38.1 among those receiving medical ther-

**Figure 1. Electrode Implantation for Deep-Brain Stimulation.**
The lead for deep-brain stimulation is implanted in either the subthalamic nucleus or the internal segment of the globus pallidus. The lead passes through a burr hole in the skull. Attached to the lead is a connecting wire, which is tunneled under the skin of the scalp and neck to the anterior chest wall, where it is connected to an impulse generator.
apy.27 And in another U.S. trial, involving 136 patients, the duration of “on” time at 3 months was 11.2 hours per day with subthalamic deep-brain stimulation versus 8.9 hours per day in the control group, which underwent electrode implantation without activation.28

**Clinical Use**

Deep-brain stimulation was approved by the Food and Drug Administration (FDA) in 2002 “as an adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson’s disease that are not adequately controlled by medication.” Most centers select patients for deep-brain stimulation on the basis of the nature of the patient’s symptoms and the likelihood of a response to the therapy; Table 1 summarizes important characteristics of potential candidates. Typically, levodopa-responsive symptoms, tremor, on–off fluctuations, and dyskinesia are most likely to improve with deep-brain stimulation, whereas impairments in gait, balance, and speech are less likely to improve and may in some cases worsen. Patients should be considered for deep-brain stimulation only if adequate trials of multiple medications for Parkinson’s disease (e.g., carbidopa–levodopa, dopamine agonists, monoamine oxidase inhibitors, and amantadine) have been unsuccessful.

If medication adjustments do not control disabling symptoms, screening for deep-brain stimulation is a reasonable next step.22 Screening is a multidisciplinary process that includes a neurologist, a neurosurgeon, a neuropsychologist, and possibly other health professionals. Interdisciplinary discussions follow screening and address risk–benefit profiles and treatment approaches.17,33,34

The standard approach to electrode implantation for deep-brain stimulation requires detailed
brain imaging before the procedure. Computed tomography (CT) or magnetic resonance imaging (MRI) is performed to delineate the target, and computer software is used to establish the location of the target by registration to a frame mounted on the patient's head or to fiducial markers previously placed on the skull.

In most cases, general anesthesia is not used during electrode implantation. Parkinson's medications are stopped 12 hours before the procedure, and the patient remains awake during the procedure for assessment of physiological recordings and behavioral responses. Anesthesia may be required in selected cases (e.g., in children and in adults with severe anxiety). CT or MRI that is performed on the day of the procedure is registered to the head frame in order to reestablish the target location and to set a trajectory that will avoid blood vessels.

A burr hole is created in the skull for the insertion of microelectrodes and a quadripolar deep-brain stimulation electrode. Microelectrodes can be used to obtain electrophysiological recordings, which may reveal characteristic neuronal signals of the specific brain target. In addition, the response of the recorded signal to passive movement of a limb can confirm an association with motor function. A physiological response to a light directed into the eyes can also aid in determining the location of the optic tract in cases in which the globus pallidus interna is targeted. Once the stimulation lead has been placed, therapeutic stimulation can be delivered through the lead to assess responses in tremor, rigidity, and bradykinesia, as well as to assess the thresholds necessary to evoke side effects. Some centers use real-time MRI during the procedure as an alternative approach for targeting and verification.

When the stimulation lead has been appropriately positioned and tested, it is anchored to the skull with a fixation device. A connecting cable is then attached to the lead and tunneled under the skin of the scalp and the neck to the anterior chest wall, where a subcutaneous pocket is created for the insertion of an impulse generator. Many centers place the connecting cable and

Figure 3. Network Effects of Deep-Brain Stimulation.
Deep-brain stimulation has broad effects on neural networks in addition to, or as a consequence of, its local influences. Motor pathways are complex, and their disturbance in Parkinson's disease is likewise far-ranging. Deep-brain stimulation modulates the feedback loops that ultimately determine motor control.
For borderline candidates, the risks and benefits of deep-brain stimulation must be carefully weighed by a multidisciplinary team.

### Table 1. Characteristics of Candidates for Deep-Brain Stimulation.

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Good candidates</td>
<td>Adequate response to dopaminergic therapy</td>
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<tr>
<td></td>
<td>Presence of on–off fluctuations</td>
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<tr>
<td></td>
<td>Dyskinesia impairing quality of life</td>
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<td></td>
<td>Medication-resistant tremor</td>
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<td></td>
<td>Reasonable cognitive function</td>
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<tr>
<td>Borderline candidates</td>
<td>Severe dyskinesia with a poor on–off dopaminergic response</td>
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<tr>
<td></td>
<td>On–off fluctuations with moderate cognitive function</td>
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<tr>
<td></td>
<td>On–off fluctuations with a poor on–off dopaminergic response</td>
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<tr>
<td></td>
<td>Medication-resistant tremor with moderate cognitive dysfunction</td>
</tr>
<tr>
<td></td>
<td>Medication-resistant tremor with a poor on–off dopaminergic response</td>
</tr>
<tr>
<td>Poor candidates</td>
<td>Severe dementia</td>
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<tr>
<td></td>
<td>Severe autonomic dysfunction</td>
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<td></td>
<td>Poor dopaminergic response</td>
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<tr>
<td></td>
<td>Atypical parkinsonism (e.g., corticobasal ganglionic degeneration, progressive supranuclear palsy, multiple system atrophy, and dementia with Lewy bodies)</td>
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<tr>
<td></td>
<td>Unstable psychiatric disease</td>
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<tr>
<td></td>
<td>Absence of a dedicated caregiver</td>
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* For borderline candidates, the risks and benefits of deep-brain stimulation must be carefully weighed by a multidisciplinary team.

Impulse generator in a separate procedure performed 2 to 4 weeks after the electrode insertion. The surgical wound is closed and postoperative CT or MRI is performed to ensure that the final position of the electrodes is acceptable. The patient is typically discharged from the hospital the day after the procedure, although discharge and programming procedures vary according to region and country.

Stimulation through the inserted lead is typically delayed for a few weeks after surgical implantation to allow for the resolution of brain edema around the inserted electrode. The pulse-generator settings that are used for stimulation are typically high frequency (130 to 185 Hz) with pulse widths of 60 to 120 μsec at voltages ranging from 2.0 to 5.0 V. Such settings are highly variable among patients, and frequent adjustment of the stimulation settings is usually necessary during the first few months after implantation. Concurrently, medications may be reduced in some but not all cases. The duration of the therapeutic benefit has not been clearly established, although reports suggest that patients may have sustained clinical improvement for at least 10 years.

A small number of patients may elect to undergo lesion therapy (pallidotomy, thalamotomy, or subthalamotomy) instead of deep-brain stimulation. Cost, complex hardware management, infection risk, and problems of availability, including travel considerations, have all been documented as important factors in the decision to forgo deep-brain stimulation in favor of lesion therapy. However, bilateral lesion therapy poses substantial risks, and deep-brain stimulation has the advantages of programmability and reversibility.

The costs of deep-brain stimulation vary widely. In a study reported in 2001, the cost of surgery was estimated to range from $28,000 to $50,000, with additional costs of $3,000 for device programming and adjustment. In a German study reported in 2005, the total costs of care during the first year were estimated to be approximately €21,000.

Hardware used for deep-brain stimulation is rarely removed, except in cases of infection. In a study of patients with a suboptimal response to deep-brain stimulation, common causes of such treatment failure included deficiencies in patient selection and screening, improper electrode positioning, insufficient attention to optimal device programming, and inadequate medication adjustment. Many of these problems can be rectified. Some patients may benefit from the addition of a rescue lead (a lead placed in the same brain target or another target). Some patients may require complete lead replacement. Troubleshooting is a critical aspect of the long-term management of deep-brain stimulation and has the potential to enhance outcomes.

### Adverse Effects

Among the most worrisome adverse events associated with placement of leads for deep-brain stimulation are infection and intracranial hemorrhage. In large series, rates of infection requiring further surgery have ranged from 1.2 to 15.2%. Infections most often require device removal and a period of antibiotic treatment before consideration of device replacement. In an extensive literature review, the overall rate of intracranial hemorrhage was calculated to be 5.0%; symptomatic hemorrhage occurred in 2.1% of pa-
patients, and hemorrhage causing permanent deficit or death occurred in 1.1%. Postprocedural seizures have also been reported, with an estimated incidence of 2.4% in one review of the literature. Lead fractures and other hardware-related issues are not uncommon.

A wide range of neurologic and neuropsychological adverse effects has been reported with deep-brain stimulation. Some of these effects are related to device implantation and may require electrode relocation or, in some cases, may be permanent. Others are related to electrical stimulation and may be addressed by adjustment of device programming or discontinuation of therapy.

Neurologic side effects of deep-brain stimulation include cognitive impairment, memory deficits, difficulties with speech, disequilibrium, dysphagia, and motor and sensory disturbances. Emotional or psychological side effects have included mania, depression, apathy, laughter, crying, panic, fear, anxiety, and suicidal ideation. It is important that patients be screened before and after the procedure for suicidal ideation, impulsivity (e.g., gambling, impulsive shopping, hypersexuality, or other behaviors), and the dopamine dysregulation syndrome (an addiction-like syndrome associated with the use of levodopa).

A meta-analysis revealed that the most common cognitive side effect of deep-brain stimulation was a decrement in verbal fluency. Impaired verbal fluency is characterized by communication difficulties and by problems in generating word lists. A decrease in verbal fluency is an effect of surgical electrode implantation, not an effect of stimulation.

**Areas of Uncertainty**

An important unresolved issue in the field of deep-brain stimulation is the question of when in the course of Parkinson's disease to add stimulation to the patient's treatment regimen. To answer this question, it will be necessary to develop a practical definition of early deep-brain stimulation in order to permit systematic studies of the possible benefits and risks associated with early intervention. Though several studies have revealed a robust benefit of deep-brain stimulation in younger patients, a reasonable track record has been reported for treatment in patients older than 70 years of age.

It is not clear whether there are definite advantages or disadvantages in selecting one target over another for deep-brain stimulation. In two recent randomized trials comparing stimulation of the subthalamic nucleus with stimulation of the globus pallidus interna, there were no significant differences in improvement in motor function between the two study groups. However, in the larger of these two trials, long-term follow-up showed a more rapid decline in cognitive function with treatment targeting the subthalamic nucleus than with treatment targeting the globus pallidus interna. More investigation will be required to confirm this finding.

A related question that is unresolved concerns the role of unilateral, as opposed to bilateral, deep-brain stimulation. Bilateral implantations may provide greater motor benefits and are often performed in a single procedure, although they can also be performed sequentially if clinically indicated. However, bilateral procedures are more likely to be associated with complications, including postoperative confusion, speech difficulties, and cognitive dysfunction. In addition, studies have shown that unilateral implantation can have bilateral benefits. An individually tailored approach to selection of the target (subthalamic nucleus or globus pallidus interna) and the procedure (bilateral or unilateral) may be optimal, although the criteria for such a selection process have not yet been well defined.

**Guidelines**

Evidence-based guidelines were last updated in 2006, when a formal practice guideline focused on the treatment of motor fluctuations in patients with Parkinson's disease was published by the American Academy of Neurology. On the basis of level C evidence, deep-brain stimulation of the subthalamic nucleus was endorsed for improving motor function and reducing “off” time, dyskinesia, and use of medication. One of the reasons that deep-brain stimulation was classified as having only level C evidence was the lack of a sham comparator group in the clinical trials. The evidence was not considered sufficient either to support or to refute the efficacy of deep-brain stimulation of the globus pallidus or of the ventral intermediate nucleus of the thalamus (a target used in the past but rarely used in current prac-
The practice guideline emphasized that the preoperative response to levodopa was predictive of the outcome, and it classified a preoperative levodopa challenge test as a practice recommendation on the basis of level B evidence.

**RECOMMENDATIONS**

Deep-brain stimulation is an effective therapy for carefully screened patients with Parkinson's disease who have disabling on–off fluctuations, dyskinesia, and medication-resistant tremor. The patient described in the vignette would be an ideal candidate for consideration for deep-brain stimulation. He is taking medications for Parkinson's disease every 2 hours, and despite frequent administration, he reports 6 hours of "off" time each day. Deep-brain stimulation typically improves "off" time by an average of 4 to 6 hours. Though the patient reports an excellent response to medications, an on–off dopaminergic test should be performed. His symptoms are largely right-sided, and he would therefore be a candidate for left-sided deep-brain stimulation. If his symptoms progress, a second stimulator could be implanted later on the opposite side.

With regard to the choice of target, as noted above, there is concern about the possibility of greater long-term cognitive decline with treatment of the subthalamic nucleus, which may be of particular concern in this patient, given his age of 72 years. Use of the subthalamic nucleus as the target, however, may provide a greater chance for medication reduction. On the other hand, the globus pallidus interna may be an excellent choice to address dyskinesia and on–off fluctuations, and it provides greater flexibility in medication adjustments after deep-brain stimulation. Use of the globus pallidus interna may also address the concern about earlier emergence of long-term cognitive issues. Finally, the globus pallidus interna may offer an advantage if the goal is to stay with unilateral deep-brain stimulation, since a study with 3 years of follow-up showed that the likelihood of requiring a future second lead with subthalamic nucleus implantation was greater by a factor of 5.2 than it was with globus pallidus interna implantation.

The interdisciplinary team that is evaluating deep-brain stimulation for this patient will need to carefully weigh the risks and benefits of each approach and each target. Ultimately, implantation of a unilateral deep-brain stimulator of the left globus pallidus interna may provide the optimal risk–benefit ratio for the patient.
58. Alberts JL, Okun MS, Vitek JL. The persistent effects of unilateral pallidal


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