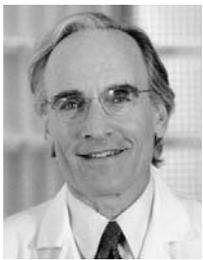


Deep Brain Stimulation in Parkinson Disease:

Important Information for Patients and Families



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Deep brain stimulation (DBS) is a well-established treatment option for Parkinson disease (PD). It is also used in other movement disorders such as essential tremor, tremor due to multiple sclerosis, tremor from stroke, and dystonia. Several brain regions targeted for DBS lie in deep motor structures in the brain known as the basal ganglia. Subthalamic (STN) and globus pallidus (GPi) DBS are used for treatment of PD; thalamic DBS is used for essential and other tremors, and globus pallidus DBS is used for generalized dystonia. DBS is unique in improving PD symptoms, reducing dyskinesia and allowing for a reduction of antiparkinson medications following surgery.

Patient Selection

DBS should only be considered for patients with PD who have displayed a very clear and dramatic response to L-dopa. The only exception to this rule is patients with tremors who may respond to DBS. DBS is not indicated for patients with less treatment-responsive forms of parkinsonism, known as “atypical parkinsonism,” due to multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, or accumulated small strokes. In one study of patients who failed to respond to DBS, 25% were given an incorrect diagnosis before surgery. Although differentiation of PD from atypical parkinsonism may be difficult early in the disease, it becomes clearer in advanced stages when surgery is considered.

When the motor fluctuations and involuntary movements of advanced stage Parkinson cannot be managed with adjustments of L-dopa or other antiparkinson medications, but the patient remains L-dopa responsive, DBS may provide an alternative. Motor fluctuations are swings in response

to L-dopa over the course of the day which appear in more advanced stages of the disease. In some cases, these movements may occur as soon as 5–10 years after beginning treatment with L-dopa. L-dopa motor fluctuations include “wearing-off” effects, “delay on” effects, and “no-on” effects (Table 1). The latter two effects are typically due to the prolonged wearing-off effect preceding the next dose. Involuntary movements or dyskinesias include peak dose dyskinesia, diphasic dyskinesia, on-period dystonia (usually peak dose dystonia), and painful off-period dystonia (Table 2). Motor symptoms (other than tremor) unresponsive to L-dopa therapy and non-motor symptoms are not indications for surgery as they would not be expected to improve after DBS.

Studies show DBS is superior in efficacy than the best available medical therapy for advanced PD with motor fluctuations. Even when DBS adjustments have been attempted by the treating neurologist, further efforts to maximize response to medications by an experienced movement disorders specialist are worth exploring. Such efforts include adjustments in the dosage and frequency of L-dopa administration, use of dopamine agonists (e.g., pramipexole, ropinirole, pergolide, apomorphine injections), use of COMT inhibitors (e.g., entacapone, tolcapone) and MAO inhibitors

TABLE 1: MOTOR FLUCTUATIONS
in patients with advanced Parkinson disease.

(e.g., selegiline, rasagaline) to prolong L-dopa doses, and the use of amantadine for suppression of dyskinesias or anticholinergic drugs (e.g., trihexiphenidyl) to suppress dystonia.

To evaluate candidates for DBS, you need first-hand observation of the response to L-dopa performed on an outpatient basis. Patients should be observed and examined in the morning following an overnight withdrawal of medication. This is referred to as the “practical off” state and allows for documentation of the patient’s severity of parkinsonism while off medication. The maximal response to L-dopa should be documented and quantified using a standard rating scale such as the motor portion of the Unified Parkinson’s Disease Rating Scale (UPDRS, part III). This may be done either by having the patient take his or her usual morning dose or a dose 50% higher than the usual dose in order to ensure maximal response. Immediate-release L-dopa should be used for this purpose. The patient’s other antiparkinson medications should also be taken. In patients with complex motor fluctuations varying throughout the day, it is also helpful to carry out serial observations as the patient cycles through at least two doses of L-dopa over several hours.

To be a suitable DBS candidate, a patient should exhibit significant motor disability while in the “off”

Type	Features
<ul style="list-style-type: none"> • Wearing-off effect • Delayed on effect • No on effect 	<ul style="list-style-type: none"> L-dopa benefit wears off in less than four hours L-dopa effect fails to begin for more than one hour L-dopa effect fails to appear due to wearing-off of previous dose

state with a UPDRS motor score of approximately 30 or more and improvement in motor score by at least 50% following administration of L-dopa. However, each case should be assessed individually. It is important for the patient to understand that, with the exception of tremor, individual motor signs unresponsive to medication are unlikely to respond to DBS. This is particularly true for patients with L-dopa resistant midline signs such as gait disturbance, postural instability, freezing, and falls.

Non-motor signs of PD such as cognitive impairment, depression, and anxiety should be carefully evaluated preoperatively with formal neuropsychological testing and, in selected cases, by formal psychiatric interview. Significant cognitive deficits and inadequately treated depression or anxiety are contraindications to surgery as they may be exacerbated following the surgery and may interfere with postoperative stimulator programming. Drug-induced visual hallucinations or psychosis are special considerations that may or may not exclude a patient from surgery. Sometimes, they are indicative of current and future cognitive decline. If considering DBS surgery, an individual’s non-motor signs should

have the following characteristics: (1) they are relatively mild; (2) they are entirely drug-induced; (3) they can be eliminated before surgery by reducing antiparkinson drugs; and (4) the neuropsychological testing shows no major cognitive deficit to make DBS a reasonable option. Since a reduction in antiparkinson medication dosage postoperatively is likely, drug-induced hallucinations should not recur following surgery unless the patient has a progressive dementia. Greater reductions in medications have been realized with the STN target.

Surgery and Postoperative Management

In most centers, DBS is carried out as a staged procedure in which cerebral electrode implantation is performed under local or no anesthesia followed by placement of the pulse generators and subcutaneous lead extensions under general anesthesia one week later. We recommend waiting four weeks after electrode implantation before initiating programming. During this time antiparkinson medications remain unchanged. Following the procedure, some patients enjoy a “honeymoon” period with temporary improvement lasting from several days to a couple of weeks.

TABLE 2: INVOLUNTARY MOVEMENTS
in patients with advanced Parkinson disease.

Type	Features
<ul style="list-style-type: none"> • Peak dose dyskinesia • Square wave dyskinesia • Diphasic dyskinesia • Off-period dystonia • Peak dose dystonia 	<ul style="list-style-type: none"> Rapid involuntary movements occurring an hour after L-dopa Continuous dyskinesia between each dose of L-dopa Peak dose dyskinesia followed by dyskinesia as L-dopa wears off Painful muscle cramping when L-dopa wears off Painful muscle cramping at peak L-dopa effect

Both DBS and L-dopa treatment may cause dyskinesias and abnormal postures. During postoperative management, stimulation is increased while L-dopa dosage is reduced.

Care should be taken to avoid lowering L-dopa dose too rapidly. Particularly in younger patients, L-dopa can appear to have a beneficial effect on mood. Lowering L-dopa dose can result in disturbing subjective symptoms while motor function appears good to both the physician and family. Although motor function may appear normal, the patient may insist they are “off” and require more medication. These symptoms usually respond by raising L-dopa doses closer to preoperative levels.

Benefits

Most patients achieve a satisfactory outcome following DBS three to six months after programming (Table 3). At this point, fewer programming visits are necessary and the patient achieves equilibrium in motor function. Only a minority of patients is able to manage without L-dopa therapy. Some patients with short-duration L-dopa responses preoperatively may experience a wearing-off effect at similar intervals postoperatively. However, these are typically less abrupt, less severe, and better tolerated than before surgery. Patients also experience less early

morning slowness and stiffness due to maintained effects of DBS overnight. Failed dose responses (“no on”) also disappear. Because of the sustained effect of DBS, off-period painful dystonia is alleviated. Peak dose or more continuous dyskinesia improve dramatically due to decreased L-dopa dose and to direct DBS effects. DBS provides a non-pharmacological treatment for patients.

Adverse Effects

Studies of cognitive function after DBS show little or no significant deficits attributable to DBS surgery. The most consistent abnormality is mild disturbance in word fluency identified in formal testing. Adverse behavioral effects reported following DBS are relatively uncommon. In isolated cases, hypomania, mania, laughing episodes, impulsive behaviors, hypersexuality, depression and anxiety have occurred during the first few months after surgery. In most cases, these behaviors respond to adjustments in stimulation or the electrode configuration. Depression or anxiety may require psychiatric assessment and treatment with antidepressant or anxiolytic medications. The risk of intracranial bleeding is estimated to be about 1-3% per electrode implantation. Fortunately, most of these are small. Many do not cause neurologic

disturbance and are detectable only with postoperative brain imaging. Hardware problems occur in about 5-10% of patients and include infection in the scalp or chest, breakage or failure of electrodes or their connections, and noninfectious skin erosions around the scalp electrodes. Infection is the most frequent and perhaps most worrisome side effect.

Long-term Outcomes

Several long-term studies following patients for four to five years after DBS show continued therapeutic benefit and improved quality of life. Studies are now emerging on GPi DBS. However, it is important to understand that DBS does not prevent further progression of PD. There are certain neurologic disabilities which occur in patients with more advanced PD and are less responsive to L-dopa or DBS. These include gait disturbance, postural instability, freezing episodes, falls, voice impairment, dysphagia and dementia. These are generally less responsive to L-dopa or DBS and over time tend to emerge as increasing sources of disability. Current and future research is directed towards improved understanding of the causes and treatment of PD. There are several large ongoing studies of STN and GPi DBS and their results should be available in the near future. ■

TABLE 3: POTENTIAL BENEFITS OF DBS	
<ul style="list-style-type: none"> • Less wearing-off effect • More predictable L-dopa responses • Improved early morning motor function 	<ul style="list-style-type: none"> • Reduction or elimination of antiparkinson medications • Less dyskinesia • Fewer painful off-period dystonic cramps

REFERENCES:

1. Deuschl G, et al. *N Engl J Med* 355:896-908, 2006.
2. Houeto JL, et al. *J Neurol Neurosurg Psychiatry* 72:701-707, 2002.
3. Krack P, et al. *N Engl J Med* 349:1925-1934, 2003.
4. Kumar R. In Tarsy D, Vitek, JL, Lozano AM, eds. *Surgical Treatment of Parkinson's Disease and other Movement Disorders*. Totowa, NJ: Humana Press 189-212, 2003.
5. Moro E, et al. *Neurology* 53:85-90, 1999.
6. Okun MS, et al. *Arch Neurol* 62:1250-1255, 2005.
7. Ostergaard K, Sunde NA. *Mov Disord* 21:624-631, 2006.
8. Siderowf A, et al. *Mov Disord* 21:746-753, 2006.
9. Simuni T, et al. *J Neurosurg* 96:666-672, 2002.
10. Welter ML, et al. *Brain* 125:575-583, 2002.