DEEP BRAIN STIMULATION IN PARKINSON’S DISEASE

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ABSTRACT

After more than a decade since its inception, deep brain stimulation has gained popularity as a surgical treatment for Parkinson’s disease and is now considered the standard of care for a subset of medically refractory patients with Parkinson’s disease. In this chapter, the authors review the mechanisms, advantages, disadvantages, targets, criteria for referral, criteria for patient selection, details of operative procedure, complications of therapy, and future directions for deep brain stimulation.

INTRODUCTION

After decades of lesion therapy, it was discovered that chronic electrical stimulation had significant and lasting benefits for the treatment of movement disorders. Deep brain stimulation (DBS) was introduced in 1987 by Benabid and colleagues for the treatment of tremor in patients with Parkinson’s disease (PD). A few short years after its introduction, high-frequency stimulation (HFS) of the globus pallidus interna (GPi), and later the subthalamic nucleus (STN), was noted to dramatically improve the symptoms of idiopathic PD. DBS is now US Food and Drug Administration (USFDA)-approved for the treatment of essential tremor (ET), PD, and generalized dystonia with a humanitarian device exemption. The treatment is now considered standard of care for a subset of medically refractory patients with PD.

MECHANISM OF ACTION

The mechanism of action of DBS is unknown. Important clues from clinical practice and research may help explain the sometimes dramatic benefits of therapy. HFS inhibits cells close to the electrical field, while fibers (afferent and efferent) tend to be stimulated. Important current ideas on the mechanism of action for DBS include:

- HFS leads to presynaptic axons’ release of inhibitory neurotransmitters, which results in inhibition of the target nucleus, whereas low-frequency stimulation leads to activation of the target nucleus.
- HFS activates afferent and efferent fibers.
- HFS leads to disruption or stabilization of the neuronal firing patterns in the target area by inducing decay at downstream synapses.
- Plastic changes occur in the downstream networks as a result of chronic stimulation.
- HFS leads to desynchronization of the network oscillations at the level of the target nucleus.
- Depolarization blockade and channel blocking may occur, in which stimulation results in alteration of voltage-gated currents that block the neural output near the...
stimulating electrode (Beurrier et al, 2001).

- Synaptic inhibition may occur, which is inhibition of neuronal activity by activation of axon terminals that make synaptic connections with neurons near the stimulating electrode (Dostrovsky et al, 2000).
- Synaptic failure may occur, which is stimulation-induced neurotransmitter depletion resulting in efferent output failure (Urbano, 2002).
- The disrupted signal is again disrupted, which is stimulation-induced disruption of the abnormal basal ganglia circuitry (Montgomery and Baker, 2000).

Future work will determine which, if any, of these theories is correct (Dostrovsky and Lozano, 2002; Grill et al, 2004; Lozano et al, 2002; McIntyre et al, 2004a; McIntyre et al, 2004b; Vitek, 2002b). In summary, HFS produces a functional lesion in a selected brain target region.

### DIFFERENCES BETWEEN LESION THERAPY AND DEEP BRAIN STIMULATION

DBS is often compared with brain lesioning (pallidotomy, thalamotomy, subthalamotomy). The main advantages of DBS over lesioning include reversibility of the procedure, the ability

#### TABLE 2-1

| Advantages | Disadvantages |
|---|---|
| Deep brain stimulation (DBS) is a reversible procedure. If at a future date a better treatment becomes available, the device can be removed without any permanent neurological sequelae. | DBS is more expensive compared with lesioning and requires more patient commitment and follow-up visits at specialized centers for optimization. This is problematic for individuals who live at a considerable distance from a center or for patients living in developing countries where DBS is not available. However, because of the medication reduction seen in bilateral subthalamic nucleus stimulation studies over a period of 5 to 7 years, the overall cost is less. |
| The efficacy of DBS is comparable to surgical lesioning (pallidotomy) in cases of unilateral brain stimulation and is superior in efficacy and side effects when bilateral devices are placed.* Bilateral surgical lesioning is no longer performed because of the unacceptably high rate of side effects. | Hardware-related complications, including lead migration, lead fracture, extension erosion, extension fracture, and implanted pulse generator malfunction, can occur in as many as 26% of the procedures. All of these are easily manageable but require a specialized center to handle them. |
| The lead settings or DBS electrodes can be adjusted; the present design allows thousands of possible combinations of settings by adjusting the electrode contact, voltage, frequency, and pulse width. | A risk of infection occurs in 2.5% to 3.7% of patients and requires removal of the device.\* |

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*Esselink RA, de Bie RM, de Haan RJ, et al. Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: a randomized trial. Neurology 2004;62:201–207.

1Charles PD, Padaliya BB, Newman WJ, et al. Deep brain stimulation of the subthalamic nucleus reduces antiparkinsonian medication costs. Parkinsonism Relat Disord 2004;10:475–479.

2Meissner W, Schreiter D, Volkmann J, et al. Deep brain stimulation in late stage Parkinson’s disease: a retrospective cost analysis in Germany. J Neurol 2005;252:218–223.

3Lyons KE, Wilkinson SB, Overman J, Pahwa R. Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures. Neurology 2004;63:612–616.

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to program the stimulator, and the ability to perform bilateral procedures without inducing pseudobulbar and other deficits (Okun and Vitek 2004). These differences are summarized in Table 2-1.

**TARGETS FOR DEEP BRAIN STIMULATION IN PARKINSON’S DISEASE**

Currently STN and GPi are the preferred brain targets for the treatment of medication-refractory PD. While each has advantages, particularly in the treatment of specific symptoms, there remains no consensus as to which target is superior. Both have the potential to improve the cardinal features of PD, including tremor, bradykinesia, rigidity, gait dysfunction, and postural instability (Rocchi et al, 2004). Additionally, both are known to reduce on–off fluctuations, dyskinesias, and dystonia. While some studies have concluded that STN DBS was slightly superior in improving motor scores, tremor, and bradykinesia (Deep Brain Stimulation for Parkinson’s Disease Study Group, 2001; Krack et al, 1998; Peppe et al, 2004), others have not shown significant differences (Burchiel et al, 1999; Vitek, 2002a). The marked clinical improvement usually seen with bilateral STN stimulation is shown in **Case 2-1**. Bilateral STN stimulation does seem to have an advantage over GPi in allowing medication reduction, which can also indirectly result in a long-term cost savings (Charles et al, 2004; Meissner et al, 2005). Because of its smaller size, STN has on average a lower voltage requirement, which may provide an advantage in terms of improving battery life. Dyskinesia management, however, may be slightly superior with GPi stimulation, which provides a more direct “antidyskinetic” effect (**Case 2-2**).

Additionally, many mood and cognitive side effects have been reported with STN DBS, and their presence has raised questions regarding safety in individual patients, particularly elderly persons and those with cognitive impairment. To date, no head-to-head trials on which to base selection of target have been done. Both targets are USFDA approved, and both are efficacious (Okun and Foote, 2005).

The thalamic target (ventralis intermedius nucleus or VIM) has been found to be efficacious in alleviating PD tremor but has not been effective in treating other PD symptoms, including bradykinesia, rigidity, dyskinesias, and postural instability (Benabid et al,

**Case 2-1**

A 70-year-old right-handed man with a history of PD for 12 years presents with worsening symptoms of PD. He was initially optimally managed with medications. Following 1 year of aggressive treatment, his symptoms of tremor, bradykinesia, and gait dysfunction were not amenable to control without causing disabling dyskinesia. He was evaluated for DBS by a multidisciplinary team. His motor Unified Parkinson Disease Rating Scale (UPDRS) scores following levodopa challenge showed an improvement from 30 to 18, and he underwent staged bilateral STN stimulation. His 1-year postsurgery UPDRS scores in an off-medication state showed an improvement of 53% with a significant decrease in off time and dyskinesias (**Video Segment 2**).

**Comment.** This case, as well as the video segment, is an example of the marked improvement seen in patients with PD following DBS.
1987; Benabid et al., 1996; Koller et al., 1997; Limousin et al., 1999; Ondo et al., 1998). VIM nucleus DBS has been demonstrated to be superior in efficacy in improving activities of daily living in comparison with unilateral thalamotomy for PD tremor, although there may be reasons to opt for lesion therapy. Stimulation of the thalamus has also been reported to result in delayed tremor rebound (Hariz et al., 1999). Long-lasting effect on tremor in PD with VIM nucleus DBS has been demonstrated (Benabid et al., 1996); however, the lack of effect on other PD symptoms has greatly curbed the use of this target for PD.

Recent reports suggest the paramedian pontine nucleus as a possible target for improvement of gait in Parkinsonian patients (Mazzone et al., 2005; Plaha and Gill, 2005). If it can be shown that this target improves levodopa-unresponsive gait symptoms, it may prove an important consideration for future trials.

**Case 2-2**

A 61-year-old right-handed man with a history of PD for 34 years underwent an embryonic nigral cell transplant 11 years prior to presentation. After receiving transient benefit in his PD symptoms for a year, he developed uncontrollable disabling dyskinesias, which mainly affected his right arm. These dyskinesias were present in a medication-on and -off state and have been referred to as “runaway dyskinesias.” He had worn out many pairs of pants because his right arm kept digging holes into the fabric. On presurgical testing, he showed an improvement in his motor UPDRS scores from 59 to 34 following a levodopa challenge. After unsuccessful attempts at medication optimization to control the dyskinesias, he had a DBS electrode placed in the left GPi. The reason for selecting GPi as a target instead of STN was because GPi DBS has a strong direct antidyskinetic effect compared with the effect of medication reduction when STN stimulation is utilized. The results of his DBS are shown in **Video Segment 1**. His 1-year off-medication, on-stimulation scores were 44 and on-stimulation, on-medication scores were 25. He became dyskinesia free following DBS.

**Comment.** In this patient, unilateral GPi stimulation resulted in complete control of unilateral dyskinesias that occurred as a result of embryonic cell transplantation.

**WHEN TO REFER A PATIENT FOR DEEP BRAIN STIMULATION**

DBS has proven efficacy in the treatment of the major motor symptoms of PD, including bradykinesia, rigidity, tremor, gait dysfunction, and postural instability. Long-term studies have demonstrated that the effects of DBS are sustained (Krack et al., 2003). Perhaps the most important point to remember when considering the referral of a patient is that only those symptoms that respond to levodopa (when the patient is in the best optimized on state) will respond to DBS (Charles et al., 2002). The main exception to this rule is medication-refractory tremor, which can be well controlled with DBS. Symptoms which may or may not respond to DBS are listed in **Table 2-2**. No consensus has been formed as to the appropriate timing for DBS surgery, but, in general, the procedure should be reserved for medication-responsive symptoms in non-demented patients with PD, who may...
also have tremor or on–off fluctuations. In practical terms, the patient under consideration for a surgical referral should experience one or several of the following difficulties:

- **Motor fluctuations** are seen in advanced PD, usually following 5 years or more of dopaminergic therapy. Many types of fluctuations have been described. The most common and the earliest to appear are wearing off of medication doses (predictable worsening of the parkinsonism or reaching the off state because the current dose “wears off” prior to the next scheduled dose of levodopa). As the disease progresses, these off states may become more unpredictable, and doses may last for shorter intervals. Patients may also experience delayed ons (the period between ingesting the dose of levodopa and the appearance of its positive effects), dose failures (when a dose of levodopa fails to produce any effect), on–off state (fluctuating between the on and off states), or sudden offs (an unpredictable off state that may be unrelated to the timing of the levodopa dose). A 5-year follow-up study of DBS has shown significant improvement in off-medication motor scores (Krack et al, 2003).
- Patients report a significant portion of the waking day in an off-medication state.
- **Dyskinesias** become disabling and limit levodopa dosage. DBS can decrease the severity of disability related to dyskinesias (Krack et al, 2003).
- **Quality of life** is severely affected as a result of PD, and patients have levodopa-responsive symptoms. Quality of life scores have shown an improvement with DBS in many studies (Diamond and Jankovic, 2005; Lezcano et al, 2004).
- The disease itself might not be advanced, but if the patient has

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**TABLE 2-2** Parkinson’s Disease Symptoms That Have the Best Chance to Respond to Deep Brain Stimulation

| Responsive Parkinson’s Disease Symptoms | Unresponsive Parkinson’s Disease Symptoms |
|----------------------------------------|------------------------------------------|
| Motor symptoms that respond to the best on state (on-off Unified Parkinson Disease Rating Scale examination) | Speech (may worsen) |
| R rigidity                              | Cognition                                 |
| Tremor                                 | Gait and postural instability (if not levodopa responsive) |
| Bradykinesia                            | Autonomic symptoms                        |
| Dyskinesias, dystonia (if not fixed)    | Mood and behavior: can improve or worsen |
| Motor fluctuations, including dose wearing off, on-off, and dose failures |                          |
| Pain as a result of Parkinson’s disease can sometimes respond to surgery |                          |
| Sleep, including architecture and efficiency |                          |

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disabling medication-refractory tremor (dopamine agonists, anticholinergics, and combinations have been tried) affecting activities of daily living, DBS may be indicated.

**SELECTION OF THE RIGHT SURGICAL CANDIDATE**

Selecting surgical candidates may be the single most important factor in ensuring an excellent surgical outcome in DBS. Based on the experience of many groups, as well as a limited number of publications, there is a general consensus that adequate surgical candidates should have features discussed below.

**Disease Type**

Candidates should have idiopathic PD and not a levodopa-unresponsive Parkinson-plus or atypical parkinsonian syndrome (corticobasal degeneration, diffuse Lewy body disease, multiple systems atrophy, progressive supranuclear palsy, or vascular parkinsonism). This point is critically important. Only those symptoms that respond to levodopa will be improved by DBS; therefore, patients with idiopathic PD are the best candidates. The most efficacious response following DBS is comparable to the best levodopa on state (Charles et al, 2002; Welter et al, 2002).

It is critical that the patient have a UPDRS motor score performed in an on- and off-medication state. A greater than 30% improvement in UPDRS motor scores (to a supratherapeutic dose of levodopa) is usually required for consideration of DBS candidacy. The on–off UPDRS score can also aid in judgment of the extent to which each symptom will respond to DBS. The results of the on–off testing can be used to educate patients regarding potential outcome. Some of the signs and symptoms that indicate red-flag potential contraindications for surgery are listed in Table 2-3.

**Cognition**

In general, most groups are reluctant to perform DBS in patients with PD who have moderate to severe dementia. The major reasons for excluding these patients include: (1) there is a potential for worsening; (2) patients need to be cognitively intact in order to participate in an awake surgery; and (3) patients need to be able to reliably articulate their symptoms during many DBS programming visits. A few reports have noted cognitive decline in demented patients following DBS. It is helpful if all potential DBS candidates are screened with detailed neuropsychological testing prior to surgery. The presence of primitive reflexes, ideomotor apraxia, decreased attention, and a Mini-Mental State Examination score of less than 26 can identify PD patients with dementia who may be suboptimal candidates for DBS. It is

**TABLE 2-3 Possible Red Flags for Parkinsonian Patients When Considering Deep Brain Stimulation Surgery**

- Primitive reflexes
- Supranuclear gaze palsy
- Ideomotor apraxia
- Autonomic dysfunction
- Wide-based cerebellar gait
- Mini-Mental State Examination score of <26
- Severe psychosis
- Unresponsive to levodopa

Okun MS, Fernandez HH, Pedraza O, et al. Development and initial validation of a screening tool for Parkinson disease surgical candidates. Neurology 2004;63:161–163. Copyright © 2004, AAN Enterprises, Inc.
important to differentiate PD dementia from medication-induced encephalopathy due to dopaminergic agents. This point can become difficult and may require formal neuropsychological testing on smaller dopaminergic doses.

**Age**

Studies have shown that the younger the patient, the better the chances for a good DBS outcome (Kumar et al, 1998; Welter et al, 2002). While one study reported that patients aged older than 69 years tended to have an increased cognitive risk (Saint-Cyr et al, 2000), others found no difference in the postoperative outcome in older patients (Kleiner-Fisman et al, 2003; Tavella et al, 2002). DBS surgeries are routinely performed in older age groups because in PD the average age of presentation is usually in the 60s. Older patients tend to have more cortical atrophy and therefore have an increased risk of perioperative bleeding. Age is still a relative risk factor, and there is no upper age limit. Older patients should be carefully evaluated for other comorbidities such as hypertension (which can put them at a higher surgical risk for bleeding), obstructive pulmonary disease, heart disease, and obesity (Starr et al, 1998).

**Disease Duration**

It is preferable that the disease duration be at least 5 years. This arbitrary time period allows for an opportunity to assure medication refractoriness and also a chance to visit a movement disorders specialist. Waiting 5 years also allows a reasonable time for identification or differentiation into Parkinson-plus syndromes (which may show a partial response to levodopa earlier in the disease course). Two exceptions to this rule include disabling tremor that is medication refractory and disabling dyskinesias.

**Expectations of Surgery**

One of the most important issues in DBS surgery is addressing patients’ expectations. The education by the physician should stress that only those symptoms that improve in the best levodopa on state will improve with surgery (except possibly dyskinesias and tremor). Postural instability and gait are the most difficult symptoms to treat, although recently some cases of stimulating the pedunculopontine nucleus, leading to improvement in gait and postural instability, have been reported. The pedunculopontine nucleus is, however, not currently an approved target for DBS. Bilateral DBS can improve gait and balance if these symptoms are levodopa-responsive prior to DBS placement (Charles et al, 2002; Welter et al, 2002). A useful mnemonic to educate patients appears in Table 2-4.

One of the tools that has been developed and validated for identification of adequate DBS surgical candidates is the Florida Surgical Questionnaire for Parkinson Disease (FLASQ-PD). This scale is a 5-section triage screener that includes criteria for the diagnosis of probable PD, contraindications to PD surgery, general characteristics, favorable and unfavorable characteristics, and quantification of an adequate medication trial. This screener can be administered by a general practitioner, a general neurologist, or a trained nurse (Okun et al, 2004).

**Multidisciplinary Team Evaluation**

The final selection of the DBS candidate should be based on evaluations by a multidisciplinary team, which optimally includes a movement disorders neurologist, a stereotaxic neurosurgeon, and a neuropsychologist. In many cases psychiatry, speech/
KEY POINTS:
- The decision for DBS surgery should be made jointly after evaluation by a multidisciplinary team consisting of a movement disorders neurologist, a stereotaxic neurosurgeon, and a neuropsychologist. Tools such as the Florida Surgical Questionnaire for Parkinson Disease can be used to initially triage patients.
- An ideal surgical candidate includes the following characteristics: nondemented, idiopathic PD diagnosed by a movement disorder neurologist, levodopa-responsive symptoms (greater than 30% improvement in UPDRS motor scores from an off state to an on state), an evaluation by a multidisciplinary team, and realistic expectations for the surgery.

TABLE 2-4 Patient and Physician Education Tool to Improve Perceived Outcomes of Deep Brain Stimulation Surgery

| Mnemonic: DBS in PD |
|---------------------|
| Does not cure.      |
| Bilateral DBS is often required to improve gait, although sometimes unilateral DBS has a marked effect on walking. |
| Smooths out on-off fluctuations. |
| Improves tremor, stiffness (rigidity), bradykinesia, and dyskinesia in most cases but may not completely eliminate them. |
| Never improves symptoms that are unresponsive to the patient’s best “on.” For example, if gait or balance does not improve with best medication response, it is very unlikely to improve with surgery. |
| Programming visits are likely to occur many times during the first 6 months and then as frequently as every 6 months. There will be multiple adjustments in the stimulator and in the medications. |
| Decreases medications in many, but not all patients. |

Okun MS, Foote KD. A mnemonic for Parkinson disease patients considering DBS: a tool to improve perceived outcome of surgery. Neurologist 2004; 10:290. Reprinted with permission from Lippincott Williams & Wilkins.

DEEP BRAIN STIMULATION IN PARKINSON’S DISEASE

resonance imaging (MRI) is usually performed. If the scan is done in close proximity to the surgery, it may be used for targeting; otherwise a scan will have to be repeated. Different imaging techniques can be utilized for identifying the stereotactic target. While MRI has superior resolution, it can be subject to distortional artifacts. Computed tomography (CT) has no distortions but has notably lower resolution. Some institutions address this problem by using software to fuse the MRI and CT images (MRI-CT fusion also saves time on the operative day). Ventriculography can also be used to demarcate the ventricles and ventricular margins as well as for choosing anatomical landmarks. All dopaminergic medications should be discontinued at least 12 hours prior to DBS surgery because medications may influence microelectrode recording as well as the clinical examination during the procedure. The patients are thus examined in an off state intraoperatively, and the benefit from DBS and the abnormal physiology can be more easily identified. A stereotactic head frame is placed on the patient’s head, usually under minimal general or local anesthesia. This head frame must be aligned with landmarks on the skull and needs to remain on throughout the procedure. The head frame acts as a reference system for stereotactic targeting. Stereotactic targeting is an exercise in “virtual reality” whereby virtual three-dimensional space from the patient’s brain images can be translated into the real space of the patient’s actual brain. The exercise uses reference points from the imaging (with the head frame), as well as from the coordinates on the head frame. After “virtual” targeting by use of specialized software, stereotactic coordinates are identified and the brain is converted into a mathematical Cartesian coordinate system in which swallowing, and physical therapy consultations are also useful.

OUTLINE OF THE DEEP BRAIN STIMULATION PROCEDURE

Once the patient has been selected, a high-resolution volumetric magnetic
each pixel is assigned a location. The coordinates chosen from the software can be used in the “real space” and are simply dialed in to the head frame.

Depending on the institution where DBS is performed, neurophysiological techniques can be employed to ensure accurate mapping of a stereotactic target. The techniques utilized are referred to as microelectrode recording (MER), microelectrode stimulation, and macroelectrode stimulation. The basal ganglia nuclei that are important in movement disorder surgery (STN, thalamus, and GPi) possess sensorimotor, limbic, and associative regions. These regions within regions have distinct somatotopy, meaning, for example, that face, arm, and leg can be predictably identified and mapped. In order to obtain the best possible outcome as well as avoid untoward neuropsychiatric side effects, it is important that the final electrode be placed in the sensorimotor region of these small subnuclei. Moreover, it is important to avoid some of the white matter tracts and surrounding nuclei in order to avoid side effects of stimulation, although sometimes stimulation of white matter tracts can have dramatic and positive benefits. By using MER and microstimulation techniques, one can obtain needed information and generate a three-dimensional physiological map of the target.

MER involves driving small microelectrodes (usually platinum iridium or tungsten), with an approximate tip diameter of a human hair (measured in microns), into various brain structures. The microelectrode can be used to identify individual single cell activity that may be unique to specific basal ganglia structures or regions. The information gathered from MER can be used to identify the boundaries and map regions and thereby be helpful in generating a picture of the deep nuclei and their location. An example of this is illustrated in Figure 2-1.

Techniques for MER vary among groups. Some prefer to use a single MER pass, while others use multiple passes to generate enough data to identify a true three-dimensional map. There is no standard MER technique, although the authors prefer true mapping.

As soon as a location for the lead is determined (a few groups do not use microelectrodes and proceed to macrostimulation following targeting), the DBS lead can be placed. Macro stimulation can be performed to check for thresholds (benefits and side effects) and is an exercise that attempts to identify the location of the lead in relation to the surrounding structures and determine usability/programmability. Common stimulation-induced side effects include contractions (twitching or tonic) of the face or limbs (internal capsule), dysarthria (corticobulbar fibers), paresthesias (may be medial lemniscus or sensory areas), unilateral pupillary changes or eye deviation (tracts involving ocular function), and phosphenes/flashes of light (optic tract region). Presence and/or absence of benefits/side effects may lead the surgeon to move the lead. The neurologist is often present throughout the procedure to aid in the electrophysiological monitoring and examination of the patient.

Controversy exists as to the role of MER in DBS. Proponents of this technique point out that accuracy at a millimeter or less can only be achieved by using MER and that this accuracy is crucial in improving outcome. Current imaging techniques cannot accurately delineate the boundaries of a target on 1-mm slices. Similarly, somatotopy and identification of the sensorimotor regions in the target nuclei can only be reliably achieved by using MER. Opponents of MER cite a slightly
higher but nonsignificant incidence of intracranial bleeding (Binder et al, 2005), prolonged surgery time, and the need for skilled expertise. A recent study on 13 patients indicated that MER could significantly improve the outcome (Chen et al, 2006). However, larger studies are needed to evaluate the role of MER in improving outcome. Groups who rely on macro stimulation without MER have less information on the exact location of structures and also may be fooled by a lesioning effect or edema at the time of electrode testing. Macro stimulation without MER is also dependant on the patient’s reports, which may present bias and also may be impacted by mild cognitive impairment present in PD. The authors believe that the benefits of MER outweigh its disadvantages, especially when expertise is available and the tool is used properly.

Postoperatively, patients are usually observed at least overnight for complications. Patients are then usually discharged on their preoperative medications and may be later brought back
for implanted pulse generator (IPG) implantation and programming after brain swelling has subsided. Some surgeons implant the lead and IPG in the same sitting. The IPG is implanted in the anterior chest wall like a pacemaker. Following IPG implantation, stimulation parameters can be adjusted and PD medications may or may not be reduced. The reduction of medications should not be the ultimate goal of surgery, but rather a balance should be sought to achieve the best results with both medications and stimulation.

Postoperative programming is carried out on follow-up visits. The objectives of postoperative programming are to:

1. Identify the optimum programming parameters. This includes identifying the best electrode contact point that can maximally stimulate the motor territory of the target while minimizing spread of the stimulus outside of this territory. Electrical parameters of the device, including polarity, frequency, pulse width, and voltage are also adjusted.
2. Monitor for surgical, hardware-related, and stimulation-related side effects.
3. Optimize medications. The goal should be to attempt to discover a balance between the stimulation settings and medications for providing the best symptom control. A common error is to aim for reducing the medications without optimizing symptom control.

COMPLICATIONS

Like all specialized surgeries, complications are closely related to the experience of the surgical team. Complications can be divided into surgical, hardware/device related, and stimulation related. These are listed in Table 2-5. While the incidence of intracranial hemorrhage ranges from 0% to 4.3% in large series, the incidence of permanent neurological deficits remains less than 1.0%. The vast majority of the infections are superficial and involve the IPG and the connecting wires (Greenberg and Rezai, 2003). There have been conflicting reports on the neuropsychological complications of DBS. While some papers report a cognitive decline in patients who underwent STN DBS, others found no cognitive deterioration (Daniele et al, 2003; Funkiewiez et al, 2004; Rodriguez et al, 2005). Impairment of verbal fluency is the most consistent problem reported following DBS. While depression has been reported with bilateral STN stimulation, the majority of the studies report a mild improvement in depression scores (Rodriguez et al, 2005; Takeshita et al, 2005). A higher rate of suicide has been reported in patients who had STN DBS (Burkhard et al, 2004); however, this claim has been recently disputed by a large study by Voon and colleagues (2006). Other mood symptoms that have been reported with DBS are listed in Table 2-5. The importance of addressing any preexisting psychiatric issues prior to the surgery cannot be overemphasized. Some reports indicate that the neuropsychological side effects may occur as a result of lead location and stimulation of limbic and associative structures (Okun et al, 2003). Cognitive and mood side effects of DBS need careful study to uncover the roles of age, diagnosis, laterality, lead placement, and premorbid conditions.

DEEP BRAIN STIMULATION FAILURES

Since the USFDA approval for DBS, the number of centers providing this
A procedure has surged. With the increase in DBS surgeries, a growing number of patients are being referred to experienced centers after unsatisfactory results from prior surgery. The factors that have been proposed as possible causes for these DBS “failures” include poor preoperative screening, incorrect diagnosis, inadequate medication trials, misplaced leads, suboptimal programming, and lack of specialized care (Case 2-3). When specialized care under a multidisciplinary team was offered to patients with DBS failures in one study, the majority (51%) were able to be salvaged with good outcomes (Okun et al, 2005). This result underscores the importance of developing a consensus on standard of care for DBS surgeries, where attention is paid to these issues.

CONCLUSION AND FUTURE DIRECTIONS

Tremendous progress has been made in the understanding of DBS. DBS has proven its safety and efficacy in long-term studies (Krack et al, 2003). Where available, DBS has become the surgical treatment of choice for medication-refractory PD. As more centers provide DBS, the need for quality control...
and the development of a standard of care increases. While DBS promises dramatic improvement in PD symptoms, it can have disappointing or even serious adverse results if careful attention is not given to patient selection; standardization of operative technique; adequate training of neurosurgeons, neurologists, and programmers; and postoperative monitoring. Many important questions remain unanswered about the surgery, including the mechanism of action. Available targets may fail to address speech, gait, and nonmotor aspects of PD, and new targets are needed. Efficacy and safety of multiple leads will need future study, and better imaging techniques are needed for target identification. Development of more durable hardware, longer battery life, improved lead designs, and increased programming options will be among the challenges facing the DBS field in the years to come.

REFERENCES

Bejjani BP, Houeto JL, Hariz M, et al. Aggressive behavior induced by intraoperative stimulation in the triangle of Sano. Neurology 2002;59:1425–1427.

A patient undergoing bilateral subthalamic nucleus (STN) stimulation developed transient aggressive behavior when the posteromedial hypothalamus was stimulated.

Benabid AL, Benazzouz A, Hoffmann D, et al. Long-term electrical inhibition of deep brain targets in movement disorders. Mov Disord 1998;13:119–125.

A review of deep brain stimulation (DBS).
Benabid AL, Pollak P, Gao D, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg 1996;84:203–214.

Ventralis intermedius (VIM) nucleus stimulation was well tolerated and effective for suppressing both parkinsonian tremor and essential tremor.

Benabid AL, Pollak P, Louveau A, et al. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol 1987;50:344–346.

An early paper, showing that thalamotomy could be combined with contralateral thalamic stimulation.

Beurrier C, Bioulac B, Audin J, Hammond C. High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. J Neurophysiol 2001;85:1351–1356.

Binder DK, Rau GM, Starr PA. Risk factors for hemorrhage during microelectrode-guided deep brain stimulator implantation for movement disorders. Neurosurgery 2005;56:722–732.

The risk of permanent neurological deficits from DBS implantation was 0.6%.

Burchiel KJ, Anderson VC, Favre J, Hammerstad JP. Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson’s disease: results of a randomized, blinded pilot study. Neurosurgery 1999;45:1375–1382.

Pallidal and STN stimulation were both safe and efficacious for the management of advanced Parkinson’s disease (PD).

Burkhard PR, Vingerhoets FJ, Berney, et al. Suicide after successful deep brain stimulation for movement disorders. Neurology 2004;63:2170–2172.

Six of 140 patients treated with DBS committed suicide. All patients experienced excellent motor outcome from the procedure. A history of severe depression and multiple DBS surgeries are predictors of suicide risk.

Charles PD, Padaliya BB, Newman WJ, et al. Deep brain stimulation of the subthalamic nucleus reduces antiparkinsonian medication costs. Parkinsonism Relat Disord 2004;10:475–479.

The cost of medical treatment was reduced by 32% in the first year after surgery.

Charles PD, Van Blercom N, Krack P, et al. Predictors of effective bilateral subthalamic nucleus stimulation for PD. Neurology 2002;59:932–934.

Younger age and levodopa responsiveness predict a favorable response to bilateral STN stimulation.

Chen SY, Lee CC, Lin SH, et al. Microelectrode recording can be a good adjunct in magnetic resonance image-directed subthalamic nucleus deep brain stimulation for parkinsonism. Surg Neurol 2006;65:253–260.

Microelectrode recording was shown to be an important adjunct in STN DBS surgery.

Daniele A, Albanese A, Contarino MF, et al. Cognitive and behavioural effects of chronic stimulation of the subthalamic nucleus in patients with Parkinson’s disease. J Neurol Neurosurg Psychiatry 2003;74:175–182.

Neuropsychological testing in 20 patients treated with DBS revealed no decline.
Deep Brain Stimulation for Parkinson’s Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson’s disease. N Engl J Med 2001;345:956–963.
Bilateral stimulation of the subthalamic nucleus or pars interna of the globus pallidus resulted in significant improvement in motor function in patients with PD where medical therapy was inadequate.

Diamond A, Jankovic J. The effect of deep brain stimulation on quality of life in movement disorders. J Neurol Neurosurg Psychiatry 2005;76:1188–1193.
A review of the effects of DBS on health-related quality of life in PD, essential tremor, dystonia, and cerebellar tremor.

Dostrovsky JO, Levy R, Wu JP, et al. Microstimulation-induced inhibition of neuronal firing in human globus pallidus. J Neurophysiol 2000;84:570–574.
Microstimulation inhibited spontaneous activity in the globus pallidus.

Dostrovsky JO, Lozano AM. Mechanisms of deep brain stimulation. Mov Disord 2002;17(suppl 3):S63–S68.
A review of proposed mechanisms of action of DBS.

Esselink RA, de Bie RM, de Haan RJ, et al. Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: a randomized trial. Neurology 2004;62:201–207.
Bilateral STN stimulation was more effective than unilateral pallidotomy in reducing parkinsonian symptoms in patients with advanced PD.

Funkiewiez A, Ardouin C, Caputo E, et al. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson’s disease. J Neurol Neurosurg Psychiatry 2004;75:834–839.
STN stimulation did not cause global cognitive decline in 77 patients with PD followed for 3 years.

Greenberg BD, Rezai AR. Mechanisms and the current state of deep brain stimulation in neuropsychiatry. CNS Spectr 2003;8:522–526.
A review of the possible mechanisms of DBS.

Grill WM, Snyder AN, Miocinovic S. Deep brain stimulation creates an informational lesion of the stimulated nucleus. Neureport 2004;15:1137–1140.
A hypothesis of the possible mechanisms of DBS.

Hariz MI, Shamsgovara P, Johansson F, et al. Tolerance and tremor rebound following long-term chronic thalamic stimulation for Parkinsonian and essential tremor. Stereotact Funct Neurosurg 1999;72:208–218.
VIM stimulation produced dramatic tremor relief in essential tremor and PD; however, at 1-year follow-up, only 70% of PD and 60% of essential tremor patients remained mostly tremor free.

Houeto JL, Mesnange V, Mallet L, et al. Behavioural disorders, Parkinson’s disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 2002;72:701–707.
Despite improvement in motor performance following STN DBS, improvement in personality traits and psychic function were not universal.
Kleiner-Fisman G, Fisman DN, Sime E, et al. Long-term follow up of bilateral deep brain stimulation of the subthalamic nucleus in patients with advanced Parkinson disease. J Neurosurg 2003;99:489–495.

Two-year follow-up of 25 patients treated with bilateral DBS revealed improvements in tremor, rigidity, and bradykinesia, and more modest improvement in axial symptoms.

Koller W, Pahwa R, Busenbark K, et al. High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. Ann Neurol 1997;42:292–299.

An early study demonstrating the efficacy of VIM stimulation in parkinsonian and essential tremor.

Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson’s disease. N Engl J Med 2003;349:1925–1934.

A 5-year follow-up of the Grenoble experience, demonstrating sustained improvement in 49 patients; severe adverse events included one large hemorrhage and one suicide.

Krack P, Pollak P, Limousin P, et al. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson’s disease. Brain 1998;121:451–457.

A small study favoring the use of the STN rather than the globus pallidus interna as a target.

Kulisevsky J, Berthier ML, Gironell A, et al. Mania following deep brain stimulation for Parkinson’s disease. Neurology 2002;59:1421–1424.

In three patients with DBS, mania occurred with stimulation caudal to the STN.

Kumar R, Lozano AM, Kim YJ, et al. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson’s disease. Neurology 1998;51:850–855.

An early study demonstrating the efficacy of DBS.

Lezcano E, Gomez-Esteban JC, Zarranz JJ, et al. Improvement in quality of life in patients with advanced Parkinson’s disease following bilateral deep-brain stimulation in subthalamic nucleus. Eur J Neurol 2004;11:451–454.

Improvements in patient and caregiver quality of life were greater than motor scale improvements.

Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. J Neurol Neurosurg Psychiatry 1999;66:289–296.

Thalamic stimulation improved parkinsonian tremor and essential tremor in 111 patients.

Lozano AM, Dostrovsky J, Chen R, Ashby P. Deep brain stimulation for Parkinson’s disease: disrupting the disruption. Lancet Neurol 2002;1:225–231.

A review of DBS.

Lyons KE, Wilkinson SB, Overman J, Pahwa R. Surgical and hardware complications of subthalamic stimulation: a series of 160 procedures. Neurology 2004;63:612–616.

Serious complications leading to permanent neurological deficit were rare after STN DBS for advanced PD; however, long-term follow-up demonstrated that hardware complications were relatively common, occurring in approximately 26% of patients.
Mazzone P, Lozano A, Stanzione, et al. Implantation of human pedunculo-pontine nucleus: a safe and clinically relevant target in Parkinson’s disease. Neuroreport 2005;16:1877–1881.

The first report of stimulation of this target in two patients with PD.

McIntyre CC, Savasta M, Kerkerkian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clin Neurophysiol 2004a;115:1239–1248.

A review of possible mechanisms of DBS.

McIntyre CC, Savasta M, Walter BL, Vitek JL. How does deep brain stimulation work? Present understanding and future questions. J Clin Neurophysiol 2004b;21:40–50.

A review of possible mechanisms of DBS.

Meissner W, Schreiter D, Volkmann J, et al. Deep brain stimulation in late stage Parkinson’s disease: a retrospective cost analysis in Germany. J Neurol 2005;252:218–223.

By the second year postoperative, total treatment costs were decreased by 54%.

Montgomery EB, Baker KB. Mechanisms of deep brain stimulation and future technical developments. Neurol Res 2000;22:259–266.

A review of possible mechanisms of DBS.

Oh MY, Abosch A, Kim SH, et al. Long-term hardware-related complications of deep brain stimulation. Neurosurgery 2002;50:1268–1274.

In this single-surgeon series, complication rate per electrode year was 8.4%.

Okun MS, Fernandez HH, Pedraza O, et al. Development and initial validation of a screening tool for Parkinson disease surgical candidates. Neurology 2004;63:161–163.

A clinically useful tool for evaluating patients for surgery.

Okun MS, Foote KD. A mnemonic for Parkinson disease patients considering DBS: a tool to improve perceived outcome of surgery. Neurologist 2004;10:290.

Okun MS, Foote KD. Subthalamic nucleus vs globus pallidus interna deep brain stimulation, the rematch: will pallidal deep brain stimulation make a triumphant return? Arch Neurol 2005;62:533–536.

A comparison of the pros and cons of each target.

Okun MS, Green J, Saben R, et al. Mood changes with deep brain stimulation of STN and GPi: results of a pilot study. J Neurol Neurosurg Psychiatry 2003;74:1584–1586.

Slight movement dorsal or ventral to the STN target may be associated with adverse mood effects.

Okun MS, Tagliati M, Pourfar M, et al. Management of referred deep brain stimulation failures: a retrospective analysis from 2 movement disorders centers. Arch Neurol 2005;62:1250–1255.

As many as half of patients who “fail” DBS can be managed with repositioning of leads or programming adjustments.
Okun MS, Vitek JL. Lesion therapy for Parkinson’s disease and other movement disorders: update and controversies. Mov Disord 2004;19:375–389.

A review of the pros and cons of lesion therapy.

Ondo W, Jankovic J, Schwartz, et al. Unilateral thalamic deep brain stimulation for refractory essential tremor and Parkinson’s disease tremor. Neurology 1998;51:1063–1069.

An early report of VIM stimulation for PD and essential tremors.

Peppe A, Pierantozzi M, Bassi A, et al. Stimulation of the subthalamic nucleus compared with the globus pallidus internus in patients with Parkinson disease. J Neurosurg 2004;101:195–200.

DBS of the STN was slightly superior to the globus pallidus interna in motor performance scores.

Plaha P, Gill SS. Bilateral deep brain stimulation of the pedunculopontine nucleus for Parkinson’s disease. Neuroreport 2005;16:1883–1887.

Stimulation of this nucleus improved gait in two patients with PD previously refractory to treatment.

Rocchi L, Chiari L, Capello A, et al. Comparison between subthalamic nucleus and globus pallidus internus stimulation for postural performance in Parkinson’s disease. Gait Posture 2004;19:172–183.

DBS restores postural and balance control.

Rodriguez RL, Miller K, Bowers D, et al. Mood and cognitive changes with deep brain stimulation. What we know and where we should go. Minerva Med 2005;96:125–144.

A review of available literature on the topic.

Saint-Cyr JA, Trepanier LL, Kumar R, et al. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson’s disease. Brain 2000;123:2091–2108.

This small study showed declines in neuropsychological tests in patients who were older than 69 years when treated.

Starr PA, Vitek JL, Bakay RA. Ablative surgery and deep brain stimulation for Parkinson’s disease. Neurosurgery 1998;43:989–1013.

A review and comparison of the two techniques.

Takeshita S, Kurisu K, Trop L, et al. Effect of subthalamic stimulation on mood state in Parkinson’s disease: evaluation of previous facts and problems. Neurosurg Rev 2005;28:179–186.

A review of the literature.

Tavella A, Bergamasco B, Bosticco E, et al. Deep brain stimulation of the subthalamic nucleus in Parkinson’s disease: long-term follow-up. Neurol Sci 2002;23(suppl 2):S111–S112.

A long-term follow-up study of 47 patients.

Urbano FJ, Leznik E, Llinas RR. Cortical activation patterns evoked by afferent axons stimuli at different frequencies: an in vitro voltage-sensitive dye imaging study. Thalamus Relat Syst 2002;1(4):371–378.
Vitek JL. Deep brain stimulation for Parkinson’s disease. A critical re-evaluation of STN versus GPI DBS. Stereotact Funct Neurosurg 2002a;78:119–131.
A comparison of the two techniques.

Vitek JL. Mechanisms of deep brain stimulation: excitation or inhibition. Mov Disord 2002b;17(suppl 3):S69–S72.
A review.

Voon V, Krack P, Lang A, et al. Frequency and risk factors for suicidal outcomes following subthalamic deep brain stimulation for Parkinson’s disease: a multicenter retrospective survey. Neurology 2006;66(suppl):195.

Welter ML, Houeto JL, Tezenas du Montcel S, et al. Clinical predictive factors of subthalamic stimulation in Parkinson’s disease. Brain 2002;125:575–583.
Younger patients and those with shorter disease duration enjoyed the greatest benefits from STN stimulation.