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Identifying candidates for deep brain stimulation in Parkinson's disease

The role of the primary care physician

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Deep brain stimulation (DBS) can improve symptoms in well-selected patients with Parkinson's disease. Primary care physicians must take into account many important issues when considering referral for DBS. The Florida Surgical Questionnaire for PD (FLASQ-PD), a 5-section screening tool that can help primary care providers identify appropriate DBS candidates, can be filled out and scored by a general practitioner, advanced clinical nurse practitioner, physician assistant, or trained nurse. Potential candidates who score well on this questionnaire can be referred for presurgical multidisciplinary evaluation at an experienced DBS implanting center.

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Learning Objectives

Upon successful completion of this educational intervention, the learner will be able to

- **Describe the basic techniques of deep brain stimulation (DBS) as a treatment option in medication-refractory Parkinson's disease.**
- **Identify appropriate candidates for DBS.**
- **List the major contraindications to DBS.**
- **State the advantages, disadvantages, and complications associated with DBS.**

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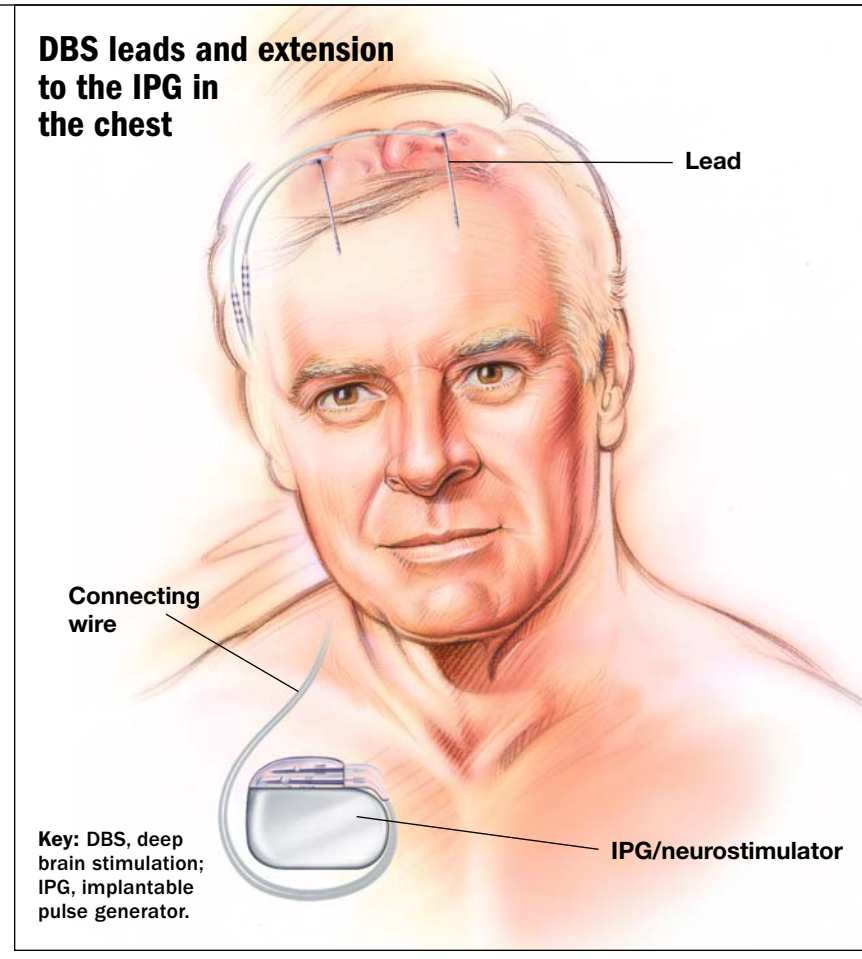
Over the past several years, deep brain stimulation (DBS) has become established as a safe and effective treatment for certain patients with medication-refractory Parkinson's disease (PD).[1-3] DBS commonly results in marked reduction in disability due to parkinsonian symptoms and dramatic improvement in quality of life for appropriately selected patients.[1,4,5] Identifying patients who are likely to benefit from DBS is a critically important first step toward successful surgical intervention.

Since most patients with PD are diagnosed and followed by primary care physicians, it is critical that essential knowledge regarding recent advances in the surgical treatment of PD be clearly and effectively transferred into the primary care setting.[5] In this article we review the information that primary care physicians need to screen their patients as potential DBS candidates. The recent introduction of the Florida Surgical Questionnaire for PD (FLASQ-PD) now enables a primary care physician to diagnose and screen potential surgical candidates in 10 minutes or less.[4]



What is deep brain stimulation?

Chronic DBS is a relatively new procedure introduced in the late 1980s.[6] It utilizes an implantable electrode that may be used in place of, or in conjunction with, ablative brain procedures such as pallidotomy or thalamotomy (thermal burning of the globus pallidus or thalamus). Appropriate candidates may include patients with PD, tremor, dystonia, or obsessive-compulsive disorder (with or without Tourette's syndrome) who are medically refractory to therapy and have no cognitive difficulties or minimal cognitive dysfunction.

DBS is an FDA-approved procedure for PD, essential tremor, and dystonia. The currently used device, manufactured by Medtronic, has 4 electrode contacts (quadripolar), and, depending on the disorder and target area, the surgeon may use variably sized contacts with different spacing arrangements. Each contact can be activated using monopolar or bipolar stimulation, and multiple settings can be adjusted to meet individual patient needs. These settings include the pulse width, frequency, and amplitude of stimulation. The DBS electrode is implanted into a specific target within the brain and attached to a programmable pulse generator. The pulse generator, or neurostimulator, is implanted in a subcutaneous pocket below the clavicle and connected to the DBS electrode in the brain via a tunneled extension cable that passes subcutaneously over the clavicle and across the posterior aspect of the neck and skull. For a summary of the advantages and disadvantages of DBS, see Table 1 (page 20).

Careful patient selection is the first and most important step for the success of DBS. No standardized criteria exist for choosing candidates, and criteria may differ depending on the targeted symptom or disorder.

Selecting surgical candidates

PD, a slowly progressive neurodegenerative disorder with cardinal manifestations of resting tremor, bradykinesia, rigidity, and gait disorder, can present many challenges for the primary care physician. Ten percent to 20% of patients with PD may be eligible for surgical procedures such as DBS. Some patients will become future candidates after medical optimization has been completed and the disease progresses. Other patients, despite medical optimization, are poor DBS candidates. Understanding who are the best can-

Table 1 Advantages and disadvantages of DBS

Advantages

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 neurologic sequelae.

The efficacy of DBS is comparable to that of 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.

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.

Disadvantages

DBS is more expensive than lesioning surgery and requires more patient commitment and follow-up visits at specialized centers for optimization. This is problematic for patients who live at a considerable distance from a center. However, the overall cost may be less because of the medication reduction seen in bilateral subthalamic nucleus stimulation studies over 5-7 y.

Hardware-related complications, including lead migration, lead fracture, extension erosion, extension fracture, and implanted pulse generator malfunction, can occur in 10%-30% of patients. All these problems are easily managed but need to be dealt with in a specialized center.

Infection occurs in approximately 2.5%-5.0% of patients and requires removal of the device.

didates and preparing those who will be future candidates should be primary goals of physicians treating PD.

Although there are no set criteria for selecting surgical candidates, a triage questionnaire was recently validated for this purpose. The FLASQ-PD[4] is a 5-section screen that includes

- Criteria for the diagnosis of probable idiopathic PD
- Potential contraindications to PD surgery
- General patient characteristics
- Favorable/unfavorable characteristics
- Medication trial information.

The scoring system was designed to assign higher scores to better surgical candidates. The highest/best possible FLASQ-PD score is 34 with 0 red flags, and the lowest/worst possible FLASQ-PD score is 0 with 8 red flags. A red flag is a sign or symptom that automatically places a patient at high risk for a surgical complication. A score of approximately 25 with no red flags indicates a potentially good surgical candidate. The questionnaire, which can be filled out and scored by a general practitioner, advanced clinical nurse practitioner, physician assistant, or trained nurse, can be downloaded at http://mdc.mbi.ufl.edu (click on "Physicians Join the DBS Fast Track Network" and then on "FLASQ-PD DBS screening tool").

Potential candidates who score well on this questionnaire may require medical optimization with a neurologist (preferably a movement disorders neurologic specialist if one is available), a neurosurgeon trained in DBS, a neuropsychologist, and possibly a psychiatrist, particularly if the patient has active psychiatric disease or a history of it. A special MRI that targets the brain ("fusible" and very thin slices) will be required; therefore, an imaging study does not need to be ordered by the primary care physician (it will probably be reordered if one is sought too early in the process). Some patients may require a speech and swallowing evaluation and possibly even physical and occupational therapy.

The best PD surgical candidates

- Have idiopathic PD (not parkinsonism, which includes other diagnoses such as multiple system atrophy, progressive supranuclear palsy, Lewy body disease, and corticobasal degeneration)
- Tend to be younger (generally, patients are younger than 69, but they may be older)
- Have a pronounced response to medication (at least 30% improvement, preferably higher)
- Are medication-refractory to symptoms (wearing-off of medications before the next dose, on-off fluctuations, dyskinesias, etc)
- Have no (or little) cognitive dysfunction.

Perhaps the most controversial aspect of patient selection is defining *unacceptable cognitive dysfunction*, especially since many patients with PD suffer from frontal and memory deficits but are quite functional in their daily lives. A general rule is that patients with PD who have multiple memory or cognitive problems and those who become disoriented frequently are poor candidates for DBS and can be made worse by surgery. The neuropsychologist can assist with the evaluation by performing a full screening visit, including tests of memory and cognition. Patients must have enough cognition to participate in an awake surgery and in multiple programming visits and medication adjustments.

Each of the items and subscales on the FLASQ-PD offers insight for choosing which patients will be appropriate for DBS surgery. A commonly held misconception is that patients with PD who cannot walk and are severely

demented are the best candidates for DBS. This is not the case. The best patients for DBS are not demented, are ambulatory, and still respond well to parkinsonian medications.[1,4,7,8] For a summary of which PD symptoms generally will or will not respond to DBS, see Table 2.

FLASQ-PD

The following review of the FLASQ-PD subscales will provide information about patient characteristics that are important for primary care physicians and geriatricians to consider when selecting PD surgical candidates.

Diagnosis of Parkinson's disease Idiopathic levodopa-responsive PD is diagnosed with the use of strict criteria, and patients selected for DBS must meet them. Diagnosis (section A of the FLASQ-PD) is contingent on the following:

- Presence of bradykinesia (slowness of movement with a loss of amplitude and often fatigue with finger taps, rapid alternating movements, and foot taps)
- Presence of 2 of the following: rigidity, 4 to 6 Hz resting tremor, and postural instability not due to visual, vestibular, cerebellar, or proprioceptive dysfunction
- Three of the following: unilateral onset, resting tremor, progressive disorder, asymmetry of symptoms, clear responsiveness to levodopa, dopamine-related dyskinesia, clinical course for at least 5 years, and responsiveness to levodopa for at least 5 years.

Absolute contraindications to DBS surgery Red flags (section B) are a collection of signs and symptoms that may represent contraindications to surgery. These include

- Presence of primitive reflexes (glabellar tap, palmar grasp, snout, suck, and palmomental reflexes that may all indicate early- or later-stage dementia)
- Supranuclear gaze palsy (trouble moving the eyes in a vertical direction, which may indicate progressive supranuclear palsy)
- Ideomotor apraxia (inability to know how to perform skilled movements such as using tools [like a hammer or scissors] or scrambling eggs); this may indicate dementia, corticobasal degeneration, or another neurodegenerative condition
- Autonomic dysfunction (early erectile dysfunction in the first year of illness; problems with orthostasis, digestion, or constipation, which can be signs of multiple-system atrophy or Shy-Drager syndrome). Idiopathic levodopa-responsive PD can produce some autonomic dysfunction, so physicians must be careful with this judgment
- Wide-based gait, which can indicate ataxia, cerebellar dysfunction, olivopontocerebellar degeneration, or another form of parkinsonism
- More-than-mild dementia (which can be worsened by surgery; patients may not be able to adequately participate in the feedback needed for their care)
- Severe psychosis (often a sign of dementia that can be made worse by surgery if not treated and controlled)
- Unresponsiveness to levodopa, or drug-naïve patients (a good response to dopamine replacement defines PD, and what responds to medications responds to surgery, so drug responsiveness is required for almost all candidates).

Before referring someone for DBS surgery, the primary care doctor should identify whether the patient has had an adequate medical trial.

General patient characteristics Several general characteristics (section C of the FLASQ-PD), if present, will im-

Table 2 Parkinson's disease symptom response to DBS

Responsive	Unresponsive
Motor symptoms that respond to the best "on" state (on-off UPDRS examination)	Speech (may worsen)
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	

Key: DBS, deep brain stimulation; UPDRS, Unified Parkinson Disease Rating Scale.

prove surgical candidacy. Age is relative with regard to being a positive or negative attribute.[9] Younger patients tend to respond better to brain surgeries and DBS,[1] but many patients with PD are in their 60s. In general, the literature suggests that age greater than 69 years may impart increased cognitive risk for patients.[10] In our practice, we routinely operate on patients into their mid-70s, and we consider older candidates based on total surgical risk (ie, we do not exclude solely on the basis of age). Nonetheless, older patients have more brain atrophy and are more likely to hemorrhage (see Table 3). They also may have friable skin that, if too thin, will erode and expose the implanted device to infection and other complications.

We usually choose patients who have had PD for at least 5 years. Many PD syndromes can mimic idiopathic cases and exhibit levodopa responsiveness early in the disease course. Waiting 5 years eliminates most of these cases from the surgical pool. In addition, a 5-year period is a reasonable amount of time to attempt to treat the patient with medications before considering surgery. In our experience, most candidates have had PD for at least 7 years prior to DBS.

On-off fluctuations are side effects that may occur when a patient with PD takes a medication (usually dopamine or a dopamine agonist) and the response is either delayed (minutes to hours) and/or it wears off before the next dose. Sometimes this problem can be addressed by adding other medications, adding doses, increasing doses, or decreasing dosing intervals. When the neurodegenerative process progresses to a state where the buffer for levodopa in the brain is depleted, side effects of medications may occur. When the therapeutic window is small (which typically is seen in moderate to severe PD), patients may experience dancelike movements when the PD medicine is "on" and be stiff and rigid when the medicine has worn off. This is referred to as *on-off fluctuations with dyskinesias* (hyperkinetic dancelike movements). Sometimes patients develop postures in which agonist muscles cocontract against antagonist muscles, resulting in abnormal and often painful foot turning, hand clenching, or other manifestations. On-off fluctuations, dyskinesias, and dystonia are all general characteristics that respond well to DBS.

One general characteristic not included on the FLASQ-PD, but important to consider, is well-controlled hypertension. Hypertension increases the surgical risks of bleeding when microelectrodes are used for mapping the brain.[11]

Favorable and unfavorable characteristics Various favorable and unfavorable characteristics (section D of the FLASQ-PD) must be considered when selecting candidates for DBS. Patients with PD may shuffle when walking, freeze, or even chase their center of gravity when ambulating (festination), all of which may lead to falling. In addition, patients may have balance dysfunction. If these symptoms do not respond to the best "on" response from levodopa, dopamine agonists, or both, when these medications have been optimized, the patient will not respond to DBS. Determining whether these symptoms respond to medications and having a frank discussion with the patient about perceived outcomes can ensure better selection of candidates.

Anticoagulants such as warfarin are relative contraindications to DBS surgery. They increase the intraoperative bleeding risk and may require temporary discontinuation prior to surgery and reinstitution afterward. We have operated on high-risk patients who required preoperative hospitalization, were converted to heparin, and then restarted on warfarin following the procedure.

Several other useful characteristics should be considered when choosing DBS candidates. PD patients with swallowing dysfunction are at risk for aspiration and other comorbid complications. Similarly, incontinence has the potential to increase infection. Severe cognitive problems and untreated affective disorders, such as depression or anxiety, have the potential to worsen as a result of surgery.[12]

Medication trials Before referring someone for DBS surgery, the primary care doctor should identify whether the patient has had an adequate medical trial (section E of the FLASQ-PD). First, and most important, the patient should exhibit a documented excellent response to levodopa. Absence of this

Table 3 Complications of DBS

Surgery-related
Seizure: 1%-3%
Hemorrhage: 1%-10%
Infection: 2%-25% (vast majority are superficial)
Permanent deficit: 0%-2%
Misplaced leads: variable, based on the center
Hardware-related
Device malfunction
Lead fracture
Lead migration
Lead disconnection
Lead erosion
Stimulation-related
Paresthesias
Muscle contractions
Dysarthria
Diplopia
Cognitive changes
Depression
Mania
Suicide
Pseudobulbar affect
Obsessive-compulsive thoughts
Anxiety/panic attacks
Aggressive behavior

Key: DBS, deep brain stimulation.

response may indicate another parkinsonian syndrome and, therefore, a poor candidate.

Many neurologists perform the Unified Parkinson Disease Rating Scale (UPDRS) when patients are in their practically defined "off-medication" state, following 12 hours without medications (usually overnight). Patients are then administered a suprathreshold dose of their medications (an extra ½-1 tablet of carbidopa/levodopa), and repeat motor testing is performed. In general, the best surgical candidates experience a change of at least 30% on this scale. Patients with a less than 30% change may not be good surgical candidates.

This on-off administration also gives the clinician a starting point for discussing what will and what will not respond to surgery, since only features of PD that respond to medications will respond to surgery. We have developed a mnemonic to help patients and physicians understand these issues (see "Mnemonic for clarifying perceived outcomes of DBS surgery").[13] We use the mnemonic to carefully review with the patient the considerations involved in DBS before and after any surgery and document the results of these discussions to prevent failures in the patient's perceived benefits of surgery. It is appropriate for the primary care physician to document levodopa responsiveness and refer the patient to a neurologist or a movement disorders neurologist for administration of appropriate screening tools like the UPDRS.

An effective medication trial requires that the primary care physician and general neurologist make various medication changes, additions, and adjustments. Increasing the frequency of a patient's levodopa or dopamine agonist dose to bid or tid administration, for example, is insufficient.

As PD progresses, medications must be adjusted, especially as the disease course changes. Medication intervals should be more frequent (strict 2-, 3-, 4-, or 5-hour intervals as needed). We prefer to define specific times to take medications and to write the schedule for patients at each visit, as opposed to instructing them to take the medication every 3 hours, for example. Doses at each interval of both levodopa and a dopamine agonist must be increased accordingly to maximize benefits and minimize side effects. It is not uncommon for a patient with PD to be taking carbidopa/levodopa, 25/100 mg q3h, with ropinirole, 3 mg, at each interval. The wearing-off effect can also be addressed by adding a dopamine extender medication such as entacapone or tolcapone (the catechol *O*-methyl-transferase [COMT] inhibitors). Amantadine can be used in cases of severe dyskinesia. If increasing doses and frequency of medications cannot correct on-off fluctuations, dyskinesia, and dystonia, surgical therapy may be considered.

Exceptional circumstances (medication refractory tremor and dyskinesia)

Occasionally, patients with PD will present with very severe tremor, but all other features of their disease will be adequately controlled with medications. In these cases, we recommend increasing doses and frequency of carbidopa/levodopa and adding a dopamine agonist and an anticholinergic (such as trihexyphenidyl or ethopropazine) to control the shaking. If this strategy fails to improve the tremor, DBS may be indicated if the surgical risk is otherwise acceptable.

Similarly, some patients who would not otherwise be surgical candidates might have dyskinesia that is so severe or violent that they should be considered on a case-by-case basis. Complex medication trials may be best performed in partnership with a neurologist.

Choosing surgical targets for DBS

Brain target selection in PD depends on many factors and may include the level of expertise of the center at which the DBS procedure is to be performed, as well as the specific symptoms of an individual patient. In most cases, the target areas of choice (both FDA approved) for improving levodopa-responsive symptoms are the subthalamic nucleus (STN) and the globus pallidus interna (GPi). On occasion, patients with tremor-predominant PD, an early disease course, and severe tremor may be appropriate for thalamic ventralis intermedius (Vim) DBS, with the caveats that tremor will likely be the only symptom treated

Mnemonic for clarifying perceived outcomes of DBS surgery

Does not cure.

Bilateral DBS is often required to improve gait, although sometimes unilateral DBS has a marked effect on walking.

Smoothes 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 be needed several times during the first 6 months, and then follow-up visits as frequently as every 6 months. There will be multiple adjustments in the neurostimulator and in the medications.

Decreases use of medications in many, but not all, patients.

and that leg tremor may or may not be improved.

Most centers implant one DBS electrode on each side of the brain in a single surgical sitting. However, unilateral DBS implantation may be all that is needed in some patients and will result in a lower-risk surgery. A staged procedure can be performed if necessary, with the second side implanted only when needed. It is hoped that several ongoing surgical studies will define which target areas are appropriate for which PD symptoms.[3]

Conclusion

The advent of DBS for PD has made available a treatment that can improve the symptoms and quality of life of patients with PD. Those who do not have a neurologist to treat them on a regular basis may be unaware of the symptomatic improvement that can be achieved with DBS therapy. It is therefore important for primary care physicians to identify and refer appropriate DBS candidates for multidisciplinary evaluations at experienced DBS centers.

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cholinergic agents recently approved, darifenacin and solifenacin, also undergo extensive CYP450 metabolism.[21, 22] In contrast, trospium is not metabolized via this pathway and is primarily eliminated unchanged. Drug-drug interaction would be an important consideration in deciding on a treatment for OAB in patients taking multiple medications.

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