Identifying Candidates for Deep Brain Stimulation for Parkinson’s Disease

Appropriate patient selection, pre-operative assessments, and careful patient counseling are all essential components to successful DBS in PD.

BY JOOHI JIMENEZ-SHAHED, MD

KEY POINTS
There are several steps in determining the appropriateness of deep brain stimulation (DBS) for Parkinson’s. First, confirm the clinical impression of idiopathic levodopa-responsive parkinsonism without atypical features to suggest secondary causes. Carefully review the DBS candidate’s medications to identify possible modifications to improve management. Inform candidates about the indications and risks/benefits of DBS. A multidisciplinary team approach involving neurologists, neurosurgeons, and neuropsychologists is ideal to review candidates for DBS and make recommendations about unilateral vs. bilateral procedures and the site of stimulation. Appropriate long-term counseling and education of the patient is essential.

A 61-year-old female with levodopa-responsive parkinsonism for eight years presents for a new patient evaluation. She is inquiring about DBS because her friends told her to ask about it and she saw a program on TV demonstrating the impact of this treatment. Her symptoms began with left-sided tremor and have progressed to involve freez ing of gait and incapacitating dyskinesias in the last two to three years. She has long-standing constipation, recent onset of mild orthostasis (especially after her morning dose of medications), and nocturnal urinary frequency. She is currently taking carbidopa/levodopa 25/250, one tablet five times daily (q 3hrs), pramipexole 1mg t.i.d., and rasagiline 1mg q.a.m. Her morning medications take about one hour to kick in, and she has painful left foot dystonia during that time. Doses typically last two to two-and-a-half hours, and she has peak-dose dyskinesias including back-and-forth head movements and facial grimacing which are particularly distressing. Her tremors recur during off times and are present bilaterally, though still worse on the left. She also has severe gait freezing with gait initiation difficulty when medications wear off. She does not go out in public much (e.g., out to eat) because she is embarrassed about the dyskinesias, and occasionally develops sudden, unpredictable off times.

She has no significant past medical history other than depression that started after her PD diagnosis, and for which she takes a selective serotonin reuptake inhibitor. She reports mild short-term memory problems, trouble multi-tasking, and has occasional difficulty thinking of the right word. The patient is examined as her medications are beginning to wear off, and is found to have bilateral rest tremors (left worse than right), mild generalized bradykine-
sia, and mild left-sided rigidity. No dyskinetic movements are apparent, and her gait is fairly normal without freezing. MoCA testing is 24/30 with deficits on visuospatial tasks (-2 points), recall (-3 points, though she identifies all items with category cues), and attention (-1 point).

When should DBS be considered in PD? Is DBS an appropriate consideration in this patient? How should this or any patient be evaluated for appropriateness of DBS? If she is a candidate, which target would be best? What are the expected outcomes of DBS?

EXPERT ANALYSIS
There are no evidence-based guidelines to help clinicians determine if or when PD patients are appropriate candidates for DBS, though decision tools exist. Generally accepted criteria include patients with idiopathic PD, a robust response to levodopa, complications of medical therapy (such as motor fluctuations or dyskinesias), lack of significant psychiatric and/or mood symptoms, no dementia, and age under 70. Less commonly, DBS is considered in PD when disabling tremor is refractory to medical therapy. Individual risk/benefit analyses and subjective considerations, such as impact on quality of life, may also be applied. For example, there are uncommon cases in which DBS may still be considered in the presence of severe, disabling, or painful dyskinesias despite evidence of cognitive impairment. DBS initially seems reasonable to consider in the patient described above, who has disabling motor fluctuations and dyskinesias, dystonic symptoms and significant gait problems during off times, and minimal cognitive symptoms.

The first step in considering DBS in PD is confirming the clinical impression of idiopathic levodopa-responsive parkinsonism without atypical features to suggest secondary causes. This is generally established by routine clinical examination, careful history taking, and brain imaging when appropriate. Our patient reports experiencing some dysautonomia, which is not unexpected in advanced idiopathic PD. The time frame for development is crucial in determining if manifestations of dysautonomia are indicative of atypical parkinsonism such as multiple systems atrophy (MSA). MSA can sometimes pose a dilemma to the treating neurologist, because it can begin with levodopa responsive parkinsonism, often with fluctuations and dyskinesias. However, the parkinsonism is quite rapidly progressive, and more florid dysautonomia occurs early in the disease course. Any patient presenting a management challenge that might seem amenable to DBS within five years of symptom onset should signal the neurologist to consider an atypical cause of his/her parkinsonism.

CRITERIA FOR DBS

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<th>Generally accepted criteria:</th>
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<tr>
<td>• Idiopathic Parkinson’s disease</td>
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<td>• Robust response to levodopa</td>
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<th>Less common criteria:</th>
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<td>• Disabling tremor refractory to medical therapy</td>
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<td>• Individual risk/benefit analyses and subjective considerations (such as QoL)</td>
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The next step is to carefully review the DBS candidate’s medications. Often, significant improvements in daily functioning can be achieved by maximizing dopamine agonist dosing or using extended release formulations, limiting levodopa to the least amount required to turn “on,” or adding amantadine. Extended release formulations of dopaminergic drugs at night can be used to improve morning off periods. Botulinum toxin injections or anticholinergic medications may be used to address the dystonic symptoms. Any or all of these strategies could be used in this patient’s case. However, these adjustments are temporizing for weeks or months, or side effects may occur such that DBS may still be the ultimate recommendation.

Third, the patient should be appropriately informed about the indications and risks/benefits of DBS. Ideally, the discussion and education process about DBS should begin at the time that the treating neurologist recognizes the presence of complications of PD therapy. The time it takes for these manipulations to run their course can be maximally utilized by the healthcare provider to prepare the patient and family for the ultimate choice to pursue DBS surgery. This can take the form of distribution of the increasingly numerous patient education materials (DVDs, monographs, books or websites), referral to a movement disorders specialist or other center with expertise in managing PD patients with DBS, or scheduling the appropriate pre-surgical evaluations when appropriate. Our patient would certainly benefit from any of these possibilities.

Once the decision is made with the patient to pursue DBS, he/she should undergo pre-operative assessments to finalize his/her candidacy for the procedure. At our center, this consists of an off/on evaluation and neuropsychologi-
that the data are “inadequate or conflicting; given current knowledge, treatment is unproven.” Since that time, three randomized and controlled trials have demonstrated superior effectiveness of DBS compared to best medical therapy (BMT)\(^{10-12}\) and one randomized study compared STN to GPi DBS.\(^{13}\) The VA cooperative study is of particular interest because the first component\(^{11}\) compared DBS to BMT regardless of site of stimulation (60 STN and 61 GPi cases), and demonstrated that in general, DBS improved motor outcomes significantly while BMT did not. In the second component of this study, which directly compared STN to GPi,\(^{13}\) the authors found essentially similar improvements in motor function, with greater reduction in medications in the STN group (31 percent vs 17.8 percent in GPi), and improvements in depression in the GPi group. Neither site of stimulation resulted in major cognitive adverse events in aggregate. Both groups experienced declines in verbal abilities, previously only well-recognized in STN DBS. Further subgroup analyses of the VA cooperative study population are eagerly awaited.

In summary, these studies tell us that either STN or GPi DBS can improve on times (up to 11 hrs/day), reduce off times, and markedly reduce dyskinesias, often while allowing reduction in medications. Recent evidence suggests that depression may improve following GPi stimulation. PD patients with prominent dystonic symptoms may also benefit from GPi stimulation. By contrast, ViM DBS is unlikely to improve any symptoms other than tremor, and is generally only useful in cases of truly tremor-dominant PD. In the long term, patients with parkinsonian symptoms other than tremor (e.g., rigidity, bradykinesia, gait changes) will still suffer from levodopa-induced dyskinesias and motor fluctuations after thalamic DBS.\(^{14}\) For this patient, GPi stimulation may be the best choice due to co-morbidities of depression (though mild) and dystonia.

Lastly, let us turn to appropriate counseling of the patient. One idea that is essential to convey to patients is that DBS is not a cure, and that it does not work any better than medications can. At our center, expectations of outcomes are guided by the results of the off/on evaluation. The off/on evaluation is conducted in the morning, in the practically defined medication “off” state, meaning that the patient has not taken any medications for PD after midnight of the night before presentation. Patients should be reminded to take their usual doses of non-PD medications. A Unified Parkinson’s Disease Rating Scale (UPDRS) is administered in this state, and once again after the patient has taken the usual dose (or sometimes more) of morning medications and has turned fully “on.” A demonstration of a minimum 30 percent improvement is generally accepted as satisfactory for pursuing DBS. The neuropsychological evaluation is performed in the medication “on” state in order to measure the DBS candidate’s emotional and cognitive well-being prior to surgery.\(^{8}\)

Patients with significant cognitive decline often fare poorly after surgery. Those with depression or anxiety are at risk of poor psychosocial adjustment after DBS and should be appropriately treated pre-DBS. Patients diagnosed with dementia are often started on acetylcholinesterase inhibitors and/or memantine and are considered inappropriate candidates for DBS.

This patient’s MoCA score are consistent with the cognitive deficits associated with PD, but should be confirmed with the neuropsychological evaluation. She also reports some depression that might warrant advancing her antidepressant therapy prior to surgery or even referring to a psychiatrist for appropriate therapy recommendations. Psychotherapy is sometimes recommended at our site concurrently with pre- and post-DBS evaluations.

Our center also uses a multidisciplinary team approach to review candidates for DBS and make recommendations about unilateral vs. bilateral procedures and the site of stimulation. The meeting is attended by neurologists, neurosurgeons, and neuropsychologists. In the absence of a committed team, individual practitioners should remain in close contact and discussion with the consulting neurosurgeon and neuropsychologist to ensure appropriate care is provided to the patient.

There are limited guidelines by which to choose the most appropriate target for DBS in PD. The American Academy of Neurology evidence-based guidelines for management of advanced PD with motor complications,\(^{9}\) does not take into consideration several recent publications on the topic of DBS compared to best medical therapy. In fact, in answer to the question: “Does DBS reduce off time, dyskinesia, medication usage, and improve motor function?”, DBS of the subthalamic nucleus (STN) was assigned a Level C for evidence, meaning that it is “possibly effective, ineffective, or harmful.” Pallidal (GPi) and thalamic (ViM) DBS were assigned a Level U for evidence, meaning that the data are “inadequate or conflicting; given current
tion. If a symptom does not improve with maximal medical therapy, it is unlikely to improve after DBS. A dedicated discussion of the anticipated benefits reduces the likelihood that patients will proceed down the DBS pathway with unreasonable expectations or that they will be disappointed afterward. Our patient should be counseled about what to expect after completing her off/on evaluation, and that medications will likely be reduced, though not eliminated. She should further be counseled that optimization of DBS settings will occur over a six-month period, that continued adjustments will be necessary over time as her disease progresses, but that axial symptoms such as cognition, speech, swallowing and balance likely to progress despite adjustments. Finally, a discussion about the actual surgical procedure and risks, choice of battery, and battery life should be incorporated. Once the target choice is determined, the reasons for and implications of this decision are reviewed with the patient and family.

Appropriate patient selection, pre-operative assessments and careful patient counseling are all essential components to successful DBS in PD. A close working relationship with the consulting neurosurgeon and neuropsychologist will further ensure that patients get the most comprehensive care. Together these aspects will set the stage for a better patient experience during post-operative care.

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