Chapter 1

Introduction

The expanding role of deep brain stimulation

William J. Marks, Jr.

Overview

Deep brain stimulation (DBS) has evolved as an important and established treatment for movement disorders, and new indications for DBS in the treatment of other neurological and psychiatric disorders are emerging. Using a fully implantable neurostimulation system, chronic DBS provides a targeted, adjustable, non-destructive, and reversible means of modulating the pathological state of brain circuits. Depending on the brain target stimulated and the disorder treated, effects may be local (at the immediate anatomical site of stimulation) or widespread (affecting distant subcortical or cortical circuits or regions).

Stimulation parameters can be programmed non-invasively to deliver the appropriate level of stimulation to the optimal anatomical nodes and networks to maximize therapeutic benefits and minimize adverse effects. The benefits of DBS compared to ablative surgery include its non-destructive nature, reversibility, and adjustability. In addition, when used bilaterally the technique does not typically produce the permanent speech, swallowing, or cognitive complications sometimes seen with ablative procedures; thus, DBS is safer for bilateral use. DBS implantation is generally safe, with serious surgical complications relatively uncommon. Adverse effects related to unintended stimulation of adjacent structures are readily reversible by altering stimulation parameters.

The DBS device and implant surgery

Deep brain stimulation uses a device with three implantable components: brain lead(s), neurostimulator(s), and extension wire(s) (Figure 1.1).

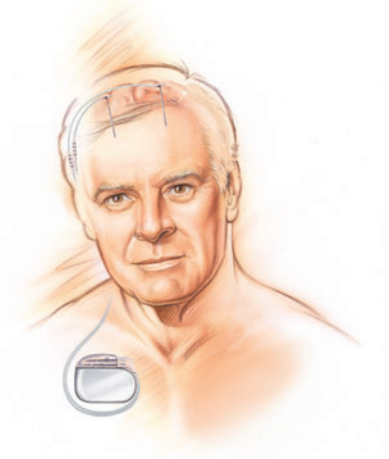

Figure 1.1 Implanted components of the deep brain stimulation (DBS) system include the DBS leads, extensions, and neurostimulator. Figure courtesy of Medtronic; used with permission.

The DBS lead, containing an array of electrodes (presently four or eight, but soon more) on its distal end, is implanted into the deep brain target using stereotactic neurosurgical techniques. Such procedures typically use image-based targeting and intraoperative physiological confirmation to accurately implant the DBS lead into the appropriate target. DBS lead implantation is often performed using local anesthesia in the awake patient to optimize the recording of physiological data during the mapping procedure, as well as to elicit the patient's report of stimulation-induced adverse effects during intraoperative test stimulation of the lead. Newer techniques harness the power of real-time interventional magnetic resonance imaging (iMRI) to guide and confirm DBS lead placement while the patient is under general anesthesia.

Following implantation of DBS leads, the neurostimulator (also called an implantable pulse generator) is implanted under general anesthesia. The neurostimulator is typically placed in the subclavicular region, although it can be located elsewhere. Bilateral

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stimulation necessitates the implantation of two single-channel neurostimulators or one dual-channel neurostimulator. Extension wires (extensions), tunneled under the skin, connect the brain leads to the neurostimulator(s). Days to weeks after device implantation, stimulation is activated. Using the DBS programmer, the clinician can select which electrodes (sometimes colloquially referred to as "contacts") on the DBS lead to use to deliver stimulation, as well as the stimulation parameters themselves (including amplitude, pulse width, and rate of stimulation).

Indications for DBS

Table 1.1 summarizes the disorders for which DBS is presently indicated.

There are currently three major movement disorders in which DBS is commonly used: essential tremor, Parkinson's disease, and dystonia. Deep brain stimulation at three different brain targets is used to treat these disorders.

For the treatment of epilepsy, two approaches have emerged: non-contingent stimulation, in which continuous or cyclical stimulation is delivered on a regular basis with the intent of suppressing seizure occurrence, and closed loop, "responsive" stimulation that delivers stimulation upon detection of electrographic seizure activity with the goal of aborting or minimizing the impact of the seizure.

Obsessive–compulsive disorder is presently the sole psychiatric condition for which regulatory approval in the US has been granted, although considerable investigation is underway to treat refractory depression with DBS.

Factors for success in DBS

In the opinion of many clinicians involved in the use of DBS, many patients who are good candidates for treatment with DBS fail to be referred to a DBS center for an evaluation to determine their suitability for this treatment option – or when they finally are referred, the patient has unnecessarily endured prolonged disability, impaired function, and compromised quality of life. Conversely, patients who are poor candidates for treatment with DBS may be referred in a "last ditch attempt to do something, when all else fails."

Table 1.1 Indications for deep brain stimulation.

Disorder	DBS target(s)	Year of FDA approval in the USA	Comments
Essential tremor and parkinsonian tremor	Ventral intermediate nucleus of thalamus (Vim)	1997	Vim thalamic target rarely used now for parkinsonian tremor, as DBS at other targets (STN and GPi) effective for tremor suppression, as well as improvement of other cardinal PD motor features
Parkinson's disease	Subthalamic nucleus (STN) or globus pallidus internus (GPi)	2002	DBS of STN tends to be used more often for PD than DBS of GPi, although there are relative merits to both targets
Dystonia	Globus pallidus internus (GPi) or subthalamic nucleus (STN)	2003 (Humanitarian Device Exemption)	The vast majority of experience in dystonia to date is with DBS of GPi, although STN DBS is being explored
Epilepsy	Seizure focus	2013	"Closed loop," responsive stimulation delivered when electrographic seizure activity is detected to abort seizures
	Anterior nucleus of the thalamus (ANT)	Pending approval in US	"Open loop," cyclical stimulation delivered on a regular basis to suppress seizure occurrence
Obsessive–compulsive disorder	Anterior limb of internal capsule	2009 (Humanitarian Device Exemption)	Target also referred to as ventral capsule/ventral striatum (VC/VS)

Notes: DBS, deep brain stimulation; FDA, Food and Drug Administration; PD, Parkinson's disease.

As experience with the clinical application of DBS has grown, several factors have emerged as vital to achieving successful outcomes for patients treated with DBS. These include the following.

- Appropriate patient selection, based on an interdisciplinary evaluation.
- Reasonable expectations on the part of the patient and their family regarding the outcome from DBS treatment.
- Accurate and uncomplicated implantation of the DBS leads into the appropriate anatomical target(s).
- Optimal programming of the DBS device, including selection and configuration of the appropriate electrode(s) on the DBS lead and choice of stimulation parameters (amplitude, pulse width, rate), in conjunction with pharmacological management.
- Adept long-term management, including management of disease progression and troubleshooting of device issues.

Note that most of these issues are non-surgical in nature. Indeed, DBS is a chronic neuromodulation therapy and not a "surgical treatment." Although it is true that expert surgical implantation of the DBS device components (especially the DBS brain leads) is necessary to achieve a successful outcome and that the surgical team is commonly involved over the long term in the care of the patient, most of the issues to be dealt with are non-surgical in nature. Typically these issues fall under the purview of neurologists, psychiatrists, nurse practitioners, nurses, physician assistants, and other non-surgeon clinicians.

DBS: a different way to think about neurological and psychiatric treatment

Neurologists, psychiatrists, and other clinicians who treat neurological or psychiatric disorders are quite familiar with pharmacological approaches to treating these conditions. The concept of using a device-based therapy to modulate brain function using electrical current may seem very foreign, however. New knowledge and skills are required to become proficient in the use of DBS. These include:

- understanding when in the course of each patient's disease process it is appropriate to consider the use of DBS;
- developing the processes for conducting and coordinating a multidisciplinary evaluation for DBS or aligning with an expert center to assist in this process;
- understanding the basic neurophysiological principles underlying the use of DBS;
- becoming familiar with the DBS device and how to optimally program it; and
- attaining comfort with the assessment of patient outcomes and determining whether patients have derived the expected benefit from DBS, and how to approach troubleshooting in those who fail to achieve the expected outcomes or lose the benefit later.

How this book can help

In teaching clinicians around the world about the various facets of DBS for many years, I have found there to be a need for a concise but comprehensive *practical* guide for clinicians interested in becoming involved with, or who are already involved in, using DBS for their patients.

Thus, this book was created to serve as a practical reference – a "go to" guide to be kept in the clinic and consulted in the course of managing patients being considered for or treated with DBS. We designed this book to address in a clear, comprehensive, and yet concise manner all of the key topics pertaining to use of DBS for clinicians.

The First Edition of this book focused on the use of DBS to treat movement disorders and was extremely well received in the United States and internationally. This Second Edition updates all of the topics included in the original book and adds dedicated chapters on the treatment of epilepsy and psychiatric disorders with DBS. In addition, with the evolution of surgical techniques for DBS lead implantation, a brand new chapter focused on interventional MRI approaches is now included.

In this new edition, Chapter 2 deals with assessing the candidacy of movement disorder patients for possible treatment with DBS. Chapter 3 focuses on the intraoperative aspects of DBS implantation surgery that are pertinent especially to the neurologist or other non-neurosurgeon clinician (although we suspect that neurosurgeons will also find this to be useful). Chapter 4, new for this edition, discusses new techniques for DBS lead implantation. Next, Chapter 5 covers the neurophysiological principles

underlying DBS, with the hope of demystifying the therapy and providing a foundation for the approach that clinicians undertake in programming DBS devices. Chapter 6 then covers the basic approaches to DBS programming that apply to all patients and all brain targets. Chapters 7, 8, and 9 go on to explore the specific approach to programming DBS devices and managing movement disorder patients who have essential tremor, Parkinson's disease, or dystonia, respectively, with an emphasis on the unique, disease-specific issues encountered by the clinician as they care for these patients. Chapter 10, brand new to this edition, focuses on DBS to treat patients with epilepsy. Another new addition, Chapter 11, covers the application of DBS for the treatment of psychiatric conditions. Chapter 12 then focuses on determining whether patients have received the expected outcomes from DBS and, if not, the approach to troubleshooting suboptimal outcomes and other complications seen in the DBS patient. Finally, Chapter 13 discusses the very practical issue of how to incorporate a DBS program into clinical practice.

We hope that this book will be a valuable resource for a wide spectrum of clinicians who encounter patients with DBS, including general neurologists, movement disorder neurologists, movement disorder fellows, neurology residents, neurosurgeons, psychiatrists, nurses, advanced practice nurses, clinical nurse specialists, nurse practitioners, physician assistants, physical therapists, and any other healthcare providers who work with patients treated with DBS.

Chapter 2

Patient selection

When to consider deep brain stimulation for patients with Parkinson's disease, essential tremor, or dystonia

Robert R. Coleman and Jill L. Ostrem

Importance of patient selection

In the use of deep brain stimulation, appropriate patient selection is a major determinant of successful outcomes.[1,2]

The following chapter details factors that should be considered when evaluating patients with Parkinson's disease, essential tremor, or dystonia for treatment with deep brain stimulation (DBS). Whenever considering DBS, the most important consideration is whether the risk of the DBS implant surgery is acceptable in light of the benefit that can be expected. Having a complete understanding of what factors predict a good outcome from DBS is critical in counseling patients, helping the clinician determine which patients are likely to realize meaningful benefit, and gauging when along the course of each patient's disease process to intervene. These factors will be discussed independently for Parkinson's disease (PD), essential tremor (ET), and dystonia. Since the risks associated with the surgery are similar across diagnoses (with a few exceptions), risk will be discussed for DBS in general.

Parkinson's disease

Who will benefit from treatment with DBS?

Parkinson's disease is a complex neurological disorder with varying signs and symptoms. A patient's age of onset, specific features and distribution of motor symptomatology, rate of disease progression, and presence or absence of nonmotor signs and symptoms can differ significantly and are important to take into consideration when determining if a patient is a candidate for treatment with DBS.

Not all patients with PD are candidates for treatment with DBS, but many will be. It is commonly estimated that, at any one time, 10–20% of patients with Parkinson's disease are candidates for DBS;[3] however, this is likely a fluid estimate, given changing practices. Additionally, it may be an under-estimate due to recent publications on use in patients with early motor complications.[4]

Although surgical procedures have been employed for decades to treat PD, practices in the modern era of neuromodulation treatment are certainly not standardized and continue to evolve as more information

Table 2.1 Summary of generally accepted criteria of deep brain stimulation candidacy for treatment of Parkinson's disease.

Inclusion criteria	Exclusion criteria
Diagnosis of idiopathic PD	Serious surgical comorbidities
Disabling or troubling motor symptoms, including motor fluctuations or dyskinesia, despite optimized pharmacological treatment	Uncontrolled psychiatric illness, including anxiety and mood disorder
Robust motor response (other than tremor) to levodopa	Dementia
Clear understanding of risks and realistic expectations from surgery	Preoperative MRI with extensive white matter changes or severe cerebral atrophy

Notes: BDI, Beck Depression Inventory; MDRS, Mattis Dementia Rating Scale; MMSE, Mini Mental Status Examination; PD, Parkinson's disease; UPDRS III, Unified Parkinson's Disease Rating Scale, Part III (Motor Subscale).

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is obtained. Despite the absence of rigorously established guidelines for DBS candidacy, a general consensus has emerged that is useful in guiding clinical practice.[5] Table 2.1 summarizes the key inclusion and exclusion criteria to be considered.

> The role of DBS is now viewed as a means of maintaining motor function before significant disability ensues – rather than being a last-resort intervention for end-stage parkinsonian patients with no other treatment options.[4]

Indications for treatment with DBS

Certainty of diagnosis

A number of factors need to be assessed in a systematic manner to determine each patient's candidacy for treatment with DBS. This treatment is most effective for patients with idiopathic PD, and it is generally not helpful for patients with other parkinsonian syndromes.[1,2,6] Thus, verification of the diagnosis is the first step in assessing a patient's candidacy for treatment with DBS (Table 2.2). Sometimes patients initially diagnosed with idiopathic PD are later found to have a different diagnosis, such as dementia with Lewy bodies (DLB), vascular parkinsonism, or a Parkinson's plus syndrome such as multiple system atrophy (MSA) or progressive supranuclear palsy (PSP).[7] Thus, making an accurate diagnosis is critical.

Table 2.2 Characteristic features of idiopathic Parkinson's disease.[10]

- Presence of at least two of the three cardinal features of parkinsonism (rest tremor, rigidity, bradykinesia)
- Asymmetrical onset of signs/symptoms
- Substantial response to levodopa or dopamine agonist
- Absence of features suggesting alternative diagnoses:
  - Prominent postural instability in the first three years after symptom onset
  - Freezing phenomena early in the first three years
  - Hallucinations unrelated to medication in the first three years of disease
  - Dementia preceding motor symptoms or in the first year
  - Supranuclear gaze palsy
  - Upper motor neuron signs on examination
  - Severe, symptomatic dysautonomia unrelated to medications
  - Documentation of a condition known to produce parkinsonism and plausibly connected to the patient's symptoms

A thorough neurological history and examination focused on each patient's initial and present symptoms and signs, rate of disease progression, response to dopaminergic therapy, and presence or absence of atypical symptoms or signs can aid in confirming or refuting the diagnosis of idiopathic PD. Longer disease duration without emergence of atypical symptoms or signs increases diagnostic certainty of idiopathic PD. As most Parkinson's plus syndromes declare themselves by 4–5 years,[8] many experienced DBS centers suggest offering DBS to patients only after this duration of symptom presence. This approach is supported by a criterion of the core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD).[9]

Probable Parkinson's disease remains a clinical diagnosis, with definitive diagnosis only possible at autopsy;[10] however, some imaging techniques may be helpful in supporting the diagnosis or differentiating it from secondary parkinsonism, Parkinson's plus syndromes, and other movement disorders. Conventional magnetic resonance imaging (MRI) is expected to be unremarkable in idiopathic PD. In some patients with parkinsonism, it may demonstrate lesions consistent with vascular parkinsonism[11] or features suggestive of a Parkinson's plus syndrome, such as the "hot cross bun" sign in MSA.[12] Transcranial ultrasound of the midbrain demonstrates hyperechogenicity in greater than 90% of PD patients with adequate bone windows.[13] However, this finding is not specific as it is also found in a minority of healthy controls,[14] and is not often utilized in routine patient care. Dopamine transporter (DAT) imaging can reliably detect striatal dopamine terminal dysfunction and help distinguish PD from ET, dystonic tremor, and psychogenic movement disorders. In its current state, it cannot reliably distinguish between PD and Parkinson's plus syndromes.[15]

Identification of motor symptoms and their disability

Once the diagnosis of PD is clinically certain, clinicians should ascertain which symptoms and signs are most troublesome or disabling for the patient

to determine whether those particular problems are likely to be improved by DBS (Table 2.3).

DBS of the subthalamic nucleus (STN) or globus pallidus internus (GPi) improves the cardinal motor features of PD, including rigidity, tremor, bradykinesia, and in some instances disturbances of gait. In addition, a reduction in motor fluctuation is commonly seen. Patients experience quality motor function ("on" time) consistently throughout their day, with fewer episodes of troubling motor symptomatology ("off" periods) and less hyperkinetic movement (dyskinesia).[4,16–22]

Motor features of PD that appear to be less responsive to DBS include speech dysfunction, swallowing difficulty, micrographia, severe postural instability, and freezing of gait.

Table 2.3 Motor symptom response to deep brain stimulation for Parkinson's disease.

Symptom	Improves	Generally does not improve
Tremor	+++	
Bradykinesia	++	
Rigidity	++	
Dyskinesia	++	
Motor fluctuations	++	
Hypophonic speech		X
Dysphagia		X
Micrographia		X
Freezing of gait, especially if occurring in the "on" state		X
Balance abnormalities of significant extent		X

Postural instability and freezing of gait can be two of the most disabling symptoms, often becoming more difficult to treat pharmacologically as PD progresses. Patients with these problems are often referred for treatment with DBS when medications have failed and complicate decision-making as it pertains to treatment with DBS. Severe disturbance of balance or gait unimproved by medication or that occurs when the patient is otherwise in a good state of medication-responsiveness (during the "on" period) appears to be especially resistant to improvement from DBS.[23,24] When these symptoms occur in the "off" period alone, some benefit may still be obtained from DBS, but the effect may not be sustained over time.[25–27]

Hypokinetic dysarthria and dysphagia can be distressing symptoms for the patient, family, and caregivers. As a general rule, DBS has limited effects on these symptoms and they can be exacerbated by spread of stimulation outside of the intended target area if DBS device programming is not optimal.[28,29]

A useful tool in gauging daily function is the PD home motor diary, a chart or electronic application in which the patient records their level of motor function periodically throughout the day (Appendix A).[30] During wakefulness, patients rate their motor function every 30–60 minutes as to whether they are "off" (slow and/or experiencing other troublesome symptoms), "on" (functioning reasonably well), or "on with troublesome dyskinesia" (experiencing excessive, involuntary movement that impedes function). Patients also indicate when medications were taken, allowing the clinician to interpret of relationships between motor function and medication timing. Such "real-time" ratings provide extremely helpful information in understanding the cumulative quantity and patterns of motor disability throughout each patient's day.

Some research protocols require patients to experience a minimum amount (e.g., three or more hours) of cumulative "off" and/or dyskinetic time each day to justify DBS treatment. In clinical practice, however, this is not always the case. In fact, a recent study demonstrated improved quality of life with DBS therapy in patients who had, on average, less than two hours of motor fluctuation per day.[4]

Tools useful to document the extent of dyskinesia include the Unified Parkinson's Disease Rating Scale (UPDRS) Part IVa (dyskinesia) score (Appendix B), the Abnormal Involuntary Movement Scale (AIMS) (Appendix C), or the Unified Dyskinesia Rating Scale (UDysRS, Appendix D).[31] To assess health-related quality of life, the Parkinson's Disease Questionnaire (PDQ-39) can also be used (Appendix E).[32]

From a careful patient history, one can develop an appreciation for the level of disability experienced by each patient. In order to justify the risk of surgical implantation of DBS leads, patients should be at a

stage in their PD in which they are experiencing impaired function. Determining what degree of impairment warrants DBS surgery should be individualized for each individual patient's circumstances.

The goal is to intervene, if possible, when the patient reaches a stage where the daily burden of parkinsonian motor symptomatology just begins to interfere with daily function, occupational activities, important leisure time pursuits, and/or basic activities of daily living.

Status of pharmacological treatment

Since DBS suppresses symptoms but does not alter disease progression, DBS is generally used to control symptoms only when reasonable pharmacotherapy fails to provide adequate and consistent relief of symptoms. To deem medical treatment sufficiently ineffective before proceeding to DBS surgery, one needs to ensure the medication regimen has been optimized for a patient's particular symptoms. Current and past PD medications and dosing schedules should be carefully reviewed. Ensuring that reasonable pharmacological treatment options have been undertaken to improve control of symptoms, motor fluctuations, and dyskinesia is essential. If not already trialed, the strategies listed in Table 2.4 can be considered to optimize treatment before considering DBS. These strategies can be employed relatively quickly to determine whether symptoms can be improved and DBS surgery can be deferred. In some patients, medications are poorly tolerated. Proceeding to surgery earlier, without attempting trials of all major medication options, may be appropriate in this situation.

Table 2.4 Strategies for optimizing pharmacological treatment of motor symptoms in Parkinson's disease before proceeding with deep brain stimulation.

1. Administer immediate-release levodopa at the appropriate dose and frequency tailored to the patient's wake/sleep, meal, and activity schedule (note that in advanced patients, controlled-release preparations of levodopa are often less consistent in their effect). This is typically five or more times a day
2. Use a dopamine agonist at appropriate doses in conjunction with levodopa as tolerated; if one agonist is ineffective or poorly tolerated, consider a trial of another agonist
3. Use a catechol-*O*-methyltransferase (COMT) inhibitor to maximize the duration of effect from levodopa
4. Use a monoamine oxidase B (MAO-B) inhibitor to increase "on-time"
5. Use an anti-cholinergic medication if the patient has severe tremor or dystonic dyskinesia
6. Use amantadine up to three times a day to treat troublesome dyskinesia
7. Consider the use of injectable apomorphine to rescue patients from severe "off" periods

Extent of dopaminergic responsiveness

The degree to which a patient is responsive to dopaminergic medication, particularly levodopa, generally predicts how responsive motor symptoms will be to DBS.[33] Levodopa responsiveness can sometimes be inferred from a careful history, but objective confirmation of levodopa responsiveness and its extent is helpful when evaluating a patient for DBS. The most widely used scale to assess motor signs in PD is the motor subscale (Part III) of the UPDRS (Appendix B).[34] A Movement Disorder Society (MDS)-sponsored revision of the UPDRS (MDS-UPDRS) is also available.[35] This new version is intended to be more comprehensive and better able to distinguish between subtle and mild motor impairments.[35] It also includes questions that expand the understanding of nonmotor symptoms.[35]

Many clinicians assess the UPDRS III score with the patient in their most symptomatic ("off") state and then again once the patient has responded to their anti-parkinsonian medication and has achieved their best motor function ("on" state). This is practically achieved by assessing the patient in the morning, following cessation of anti-parkinsonian medication for about 12 hours overnight, and then again after the patient has ingested their usual morning dose of medication (with or without extra levodopa) and derived a good response. Evaluation of the patient in the "off" state provides an instructive glimpse into the patient's motor symptoms and associated disability at its most severe (not often appreciated in a routine

office visit). It also allows for an objective comparison of the "off" and "on" UPDRS III scores, confirming the degree of responsiveness to dopaminergic medication, and can help gauge which symptoms will likely respond to DBS and to what extent.[33] By performing these measures, one derives information helpful in educating the patient and family about likely outcomes with OBS treatment.

The minimal degree of improvement after a dopaminergic challenge to be considered a candidate for DBS is not well established, although many clinicians desire at least a 30% improvement in UPDRS III score and a minimum UPDRS III score of 30/108 in the "off" state.[36] The CAPSIT-PD recommends a 33% improvement in the UPDRS III subscore or greater before recommending an interventional approach like DBS.[9] Rarely is DBS surgery offered to patients who do not demonstrate at least a 30% improvement. Exceptions may include patients who suffer from severe dyskinesia, frequent "on/off" motor fluctuations, or medication-refractory parkinsonian tremor.[37] Additionally, a levodopa challenge evaluation may be of limited use in patients who cannot tolerate typical therapeutic doses of levodopa due to adverse effects (e.g., nausea, orthostatic hypotension, fatigue). In these situations, DBS may still be considered, and patients often have excellent outcomes (personal observations).

Symptoms and signs resistant to levodopa will likely be resistant to DBS, with the notable exception of medication-resistant tremor.

We also find that videotaping each patient's preoperative examination during the "off" and "on" UPDRS III assessments provides a useful visual record of baseline motor dysfunction, which can later be reviewed postoperatively to appreciate treatment response.

Identification of nonmotor symptoms

There is a high prevalence of nonmotor symptoms (NMS) in Parkinson's disease, including cognitive, psychiatric, autonomic, sleep, and sensory symptoms. In a large Italian multicenter survey, 98.6% of patients with PD complained of at least one NMS.[38] The presence and severity of these symptoms can contribute greatly to decreased quality of life.[38] The effect of DBS on cognition and psychiatric symptoms is fairly well established. There is increasing evidence about the effect of DBS on other NMS as well.[39–42]

Cognitive status

A clear understanding of the patient's cognitive function is important when considering candidacy for DBS.

Dementia is common in PD, with prevalence increasing with advanced age and disease progression.[43] In one eight-year prevalence study, over three-quarters of PD patients developed dementia.[43] Most clinicians do not offer DBS to patients with bona fide dementia.[5,44] The presence of dementia suggests that there is more widespread disease,[45–47] which may be a marker for less robust motor response to DBS. Additionally, the presence of dementia produces practical obstacles to achieving optimal outcomes. Patients with dementia have difficulty tolerating and cooperating with the awake surgical procedures typically employed. Patients with dementia also have difficulty accurately observing and articulating their symptoms, making adjustment of DBS parameters and medications more difficult. Finally, patients with pre-existing dementia may experience a worsening of their cognitive status following DBS surgery, leading to more disability.[48]

Mild cognitive impairment (MCI) is also common in PD and increases the risk for developing dementia.[49] There is suggestion that non-demented PD patients with worse scores on cognitive tests may not have similar improvements in quality of life with DBS compared to those that scored better.[50] Although MCI itself is not an absolute contraindication to DBS, patients with more severe MCI may need additional consideration to their candidacy, DBS site, and approach as discussed later.

The MDS has published clinical diagnostic criteria for Parkinson's disease-associated dementia (PDD)[51] and mild cognitive impairment (PD-MCI).[49] To screen for PDD and PD-MCI in clinic, a Mini Mental Status Exam (MMSE) can be performed. It is generally accepted that a MMSE score of ≤ 24 is an indicator of poor candidacy for DBS surgery.[36] More recently, the Montreal Cognitive Assessment (MoCA)

has been suggested as a more appropriate cognitive screening test, as it tests a wider range of cognitive domains than the MMSE and can detect deficiencies earlier in the course of PD (Appendix F).[52,53]

Many clinicians at experienced DBS centers evaluate all patients being considered for DBS with a battery of neurocognitive tests preoperatively. Certainly, if the history or screening examination raises concerns about a patient's cognitive status, formal neuropsychological testing should be performed. Patients with PD can develop cognitive deficits in areas of executive functioning, visuospatial processing, attention and set shifting, and memory function. In the neurocognitive testing battery, it is important to include measures of general cognitive functioning, such as the Mattis Dementia Rating Scale (MDRS); measures of executive functioning and attention, such as verbal fluency tests, paced auditory serial addition tests, or the Wisconsin Card Sorting Test; measures of short- and long-term memory function; measures of visuospatial function; and measures of language function. In some instances, results from neuropsychological testing may reveal a pattern of dementia that is more compatible with Alzheimer's disease, diffuse Lewy body disease, or PSP, offering evidence against the pursuit of DBS for that patient. Some clinicians exclude patients based on an MDRS total score of $\leq$ 120–130/144,[9,36] or use a rejection criterion of an MDRS total score two or more standard deviations below the age-adjusted mean normal score, or the criterion of two or more (out of five) subtest scores that lie beyond two standard deviations.

Mood and psychotic symptoms

Patients with PD are prone to depression, anxiety, and psychotic symptoms, including hallucinations and delusions. These symptoms can be a direct result of the disease process or exacerbated by medications used to control the motor symptoms of PD. The prevalence of depression in PD patients ranges from 20% to 50%,[54] with the majority of these patients meeting criteria for anxiety as well.

The literature is conflicted on the effect of DBS on mood. Some studies suggest improvement in mood after treatment with DBS;[55,56] however, in some individuals, depression and anxiety can worsen.[57,58] Although there is no clear evidence that the presence of a pre-existing mood disorder increases the risk of postoperative disturbance in mood, it seems reasonable to assume that before proceeding with surgery, mood disorders should be identified and effectively treated.

> Furthermore, offering DBS surgery to patients with severe pre-existing depression or anxiety that does not adequately respond to pharmacological treatment may not be advisable.

The Geriatric Depression Scale – Short Form has been suggested by specialists as a useful tool for screening for depression in PD (Appendix G).[59] Also the Beck Depression Inventory (BDI), the Hamilton Depression Rating Scale, and the Montgomery and Asberg Depression Rating Scale (MADRS) have been recommended to assess depression by the American Academy of Neurology.[60] In our center, if a patient has a score of $>$ 15 on the BDI, then surgery is generally not recommended. The CAPSIT-PD recommends a score ranging from 7 to 19 on the MADRS as an exclusion criterion.[9]

Parkinson's disease patients referred for DBS treatment are also at greater risk for psychotic symptoms, as they usually have relatively advanced disease and are being treated with moderate to high doses of medications that have the potential to cause adverse psychiatric effects. Patients with active hallucinations or delusions may be at increased risk for psychiatric complications after DBS surgery. A wide range of psychiatric symptoms has been described following STN DBS surgery, including hallucinations, severe psychosis, mania, and impulsivity.[55] Many times these symptoms occur in the immediate postoperative period, when patients are hospitalized, and are transient. Cases of persistent postoperative behavioral disturbance have been reported, though, and these may be more likely to occur in patients who are prone to these problems preoperatively.[57]

> Thus, patients with significant, unresolved psychotic symptoms should probably not undergo DBS surgery.[57,61]

In many instances, reduction of anti-parkinsonian medication or addition of an atypical antipsychotic agent can improve these symptoms, with the patient then able to proceed with DBS surgery.