Rationale and Clinical Pearls for Primary Care Doctors Referring Patients for Deep Brain Stimulation

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Key Words

Deep brain stimulation · Patient selection · Criteria · Family practice · Internal medicine

Abstract

Background: Deep brain stimulation (DBS) is a surgical treatment involving the implantation of a brain lead connected to a chest-based neurostimulator similar to a cardiac pacemaker. The device can be programmed to deliver electrical impulses to neuromodulate abnormal brain circuitry in disorders such as Parkinson's disease (PD), essential tremor (ET), and dystonia. As the number of patients receiving DBS surgery increases, it will be important for primary care doctors to identify reasonable DBS candidates for referral to an experienced center. **Objective:** To provide primary care physicians with a rationale and also to provide clinically useful pearls for referral of potential DBS candidates. **Methods:** A complete PubMed review of the literature. **Results:** This review will be focused on PD and ET and will address the following issues: what are the common motor and nonmotor symptoms? What is the evidence supporting the use of DBS in PD and ET? What is the importance of a multi- or interdisciplinary DBS team for patient selection? What can be done to improve success in identifying and referring potential DBS candidates? **Conclusion:** DBS is a highly effective therapy for

select candidates with PD and ET. The most important factor influencing DBS outcome is proper patient selection. It will be critical as DBS continues to be more commonly employed for primary care doctors to select candidates from their practices as appropriate referrals to specialized centers.

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Introduction

Brain stimulation as a field has evolved over the centuries from the humble beginnings of Scribonius Largus [1] using the electric torpedo fish to treat headache and gouty arthritis to the chronic placement of a deep brain stimulation (DBS) device by the French neurosurgeon Alim Benabid [2]. The placement of a 'chronic' DBS electrode by Benabid et al. in 1987 opened a new era for the therapy. DBS is now considered an important therapy for the treatment Parkinson's disease (PD), essential tremor (ET), and dystonia, and it has been applied in a research setting for the treatment of other medication-refractory neurological and neuropsychiatric diseases [3]. US Food and Drug Administration (FDA) approval for DBS was granted in 1997 for thalamic stimulation for ET, and later in 2003 for PD-related tremor in two brain targets, i.e. the subthalamic nucleus (STN) and globus pallidus internus

(GPi). These two brain targets were shown to be effective for addressing the medication-refractory symptoms of advanced PD [4]. The late David Marsden, a British neurologist widely considered an international expert on movement disorders, was quoted as saying he observed two miracles in PD during his career. The first was the introduction of levodopa, and the second was the development of DBS [5].

The mechanism of action of DBS remains unknown; however, recent advances have shed light on the many possible changes that, in total, likely lead to the therapy's overall positive effect. DBS is thought to inhibit cells close to the stimulation field, excite fibers of passage [6, 7], and cause changes in blood flow as well as neurogenesis [8]. DBS affects astrocytes and is hypothesized to ignite a propagating calcium wave that later leads to adenosine and glutamate being dumped into the synaptic cleft [9, 10]. DBS also has been shown to change neuronal oscillations and, although it affects only a small amount of local tissue, its actual effects change on an entire neuronal network. Neuro-network modulation is what has been proposed as the most likely overall change in the brain that underpins the improved clinical symptoms observed across patients suffering from several different disease states [4].

As the evidence base for DBS has evolved, many important issues have surfaced, and these include: what operation should be performed, when to operate, who should be operated on, and, finally, why operate. As more patients undergo DBS, it will be important for clinicians, and particularly for primary care providers to recognize potentially ideal DBS candidates [11]. The primary care provider can identify and triage potential DBS candidates. Once identified, a referral should be made to an experienced multi- or interdisciplinary team [12].

In this viewpoint article, we will focus on the following DBS-related topics: what are the common motor and nonmotor symptoms? What is the evidence supporting the use of DBS in PD and ET? What is the importance of a multi- or interdisciplinary DBS team for patient selection? What can be done to improve success in identifying and referring potential DBS candidates?

What Are the Common Motor and Nonmotor Symptoms of PD and ET?

PD is a neurodegenerative disorder that results from the loss of dopaminergic cells in the substantia nigra; however, there is degeneration present in several motor

and nonmotor basal ganglia circuits. The four cardinal motor features of PD are tremor at rest, rigidity, bradykinesia, and loss of postural reflexes.

Though resting tremor is the most easily recognized symptom of PD, in approximately 25% of sufferers resting tremor will not manifest during the course of the disease. Tremors and other symptoms are typically unilateral and occur asymmetrically early in the disease. Tremor is classically 4–6 Hz, prominent in the distal extremity, and may have a characteristic supination-pronation ('pill-rolling') movement. In addition to resting tremor, most patients also manifest a mild postural tremor.

Bradykinesia refers to slowness of movement and is the most characteristic feature of PD. Assessment of bradykinesia at the bedside typically includes performing rapid, repetitive, alternating movements of the hand (finger taps, hand grips, hand pronation-supination) and heel tapping. The distinguishing feature of bradykinesia is the decrement of amplitude or 'fatigue' in movement.

Rigidity refers to increased resistance to passive movement of a joint, which is constant throughout the range of joint displacement, and is not related to the speed of joint movement. PD rigidity is typically a 'cogwheel' phenomenon, and when an examiner slowly moves the wrist or forearm he or she can appreciate a slow clicking. Distraction maneuvers, known as Froment's maneuvers, may increase rigidity and can be helpful at the bedside to appreciate especially subtle manifestations.

The fourth cardinal feature of PD is loss of postural reflexes (gait and balance issues). This feature can be examined by having a patient walk, and then by using a 'pull test'. A forward flexed posture, shuffling steps, problems turning, and freezing (motor blocks) may all be observed during the gait and balance examination [13].

Because there is no definitive biomarker for the diagnosis of PD, the diagnosis must be made based on clinical criteria [14].

Nonmotor symptoms of PD, which have been documented to occur in 88% of sufferers, are underrecognized and undertreated. These manifestations have important social implications as these symptoms have a greater impact on quality of life than do the motor symptoms. Nonmotor symptoms have been divided into neuropsychiatric symptoms (e.g. depression, anxiety), sleep disorders (e.g. REM sleep behavioral disorder, apnea), autonomic symptoms (e.g. orthostasis, constipation), sensory symptoms (e.g. olfaction, and numbness), and other manifestations [15]. Table 1 summarizes the nonmotor symptoms that may occur in PD.

Table 1. Nonmotor symptoms in PD

Neuropsychiatric symptoms	Depression, apathy, anxiety, anhedonia, cognitive dysfunction, attention deficit, hallucinations, illusions, delusions, dementia, panic attacks
Sleep disorders	Restless legs and periodic limb movements, REM behavior disorder, REM loss of atonia, non-REM sleep-related movement disorders, excessive daytime somnolence, vivid dreaming, sleep-disordered breathing
Autonomic symptoms	Bladder disturbances (urgency, frequency, nocturia, incontinence), sweating, orthostatic hypotension, erectile dysfunction
Gastrointestinal symptoms	Excessive salivation, ageusia, dysphagia, choking, nausea/vomiting, constipation, unsatisfactory voiding of the bowel, fecal incontinence
Sensory symptoms	Pain/cramps, paresthesia, olfactory disturbance, visual dysfunction (contrast sensitivity, color vision, double vision)
Other symptoms	Fatigue

Although ET has been historically described as a benign disease, recent data has suggested that, in most patients, it is progressive and disabling [16]. ET is characterized by a kinetic/postural tremor (which may be the result of abnormal of cerebellar-thalamic outflow pathways) affecting mainly the arms/hands, head, and voice, and has a frequency between 4 and 12 Hz. Postural instability and ataxic gait have also been described, and approximately 20% of patients will develop a resting tremor, usually late in the disease course. The Consensus Criteria of the Movement Disorder Society for ET have been the most frequently applied by clinicians and researchers [17].

There is growing evidence suggesting that ET patients may have significant nonmotor symptoms. These include cognitive abnormalities (memory and executive problems), a higher prevalence of psychiatric symptoms (anxiety, depression), poor sleep quality, and sensory abnormalities (olfactory deficits and hearing loss) [18]. ET is no longer being considered as a pure motor disorder and further studies of nonmotor aspects will in the near future enhance our understanding of this disease. Additionally we no longer refer to ET as 'benign' ET, since the manifestations can be highly disabling [16].

What Is the Evidence Supporting the Use of DBS in PD?

Three randomized, controlled clinical trials comparing DBS versus best medical management for advanced PD patients have been published, and all three revealed that treatment with DBS was superior to medical therapy

for improving motor function and quality of life when carefully applied to a select group of PD sufferers. We will summarize the results of each trial.

The first trial, conducted by the German Parkinson Study Group [19], reported changes in the quality of life [Parkinson's Disease Quality of Life Questionnaire (PDQ-39)] and motor function [Unified Parkinson's Disease Rating Scale (UPDRS-III)] of patients under the age of 75 who had advanced PD with severe fluctuations and possibly also dyskinesia. The primary outcome was measured at 6 months following implantation of the devices. Bilateral STN DBS was observed to provide significant and clinically meaningful improvement in both quality of life and motor function. Though the inclusion criteria allowed enrollment of patients up to age 75, those actually enrolled were relatively young, with a mean age of 60.5 years (± 7.4) and a mean duration of levodopa treatment of 13.0 years (± 5.8).

The second study was conducted by the PD SURG Collaborative Study Group [20] and reported changes in quality of life (PDQ-39) over a 1-year follow-up period. Again, the results revealed clear advantages for DBS as compared to best medical therapy. The mean age of patients enrolled into the study was 59 years (range 37–79) and the mean disease duration was 11.5 years (range 2.0–32.2).

The third trial was conducted by the CSP 468 Veteran's Administration Study Group [21] and compared dyskinesia diaries and the time spent in the 'on' state without troubling dyskinesia in patients with either STN or GPi DBS randomized versus best medical therapy over a 6-month follow-up period. Patients who received DBS

devices gained a mean of 4.6 h/day of 'on' time without troubling dyskinesia as compared to 0 h/day for patients who received only the best medical therapy. The mean age of patients enrolled into the study was 62.4 years (± 8.8) and the mean time taking PD medications was 10.8 years (± 5.4).

At the 24-month outcome for the CSP study, improvements in motor function and quality of life were reported in those randomized to either STN or GPi DBS [22]. The primary outcome of motor function change and the dyskinesia diaries were no different with the use of either brain target. These findings and the subsequent follow-up studies [23] suggested that there may be important target-specific differences, e.g. more medication reduction for STN DBS compared to GPi DBS, but possibly more cognitive issues and difficulties in long-term medication management in the STN group [22, 24].

A fourth important trial was the NIH COMPARE study [25], which examined unilateral STN DBS versus unilateral GPi DBS but did not include a medication comparison group. The study revealed no differences in the primary outcomes of mood and cognition; however, it revealed that when shifting stimulation within the targets there were target-specific differences. Additionally, the study showed that the most common cognitive deficit following DBS surgery, i.e. verbal fluency (the ability to get words out of the mouth), was likely a surgical and not a stimulation-related side effect. There were more verbal fluency deficits in the STN compared to the GPi group. The study also revealed no differences in motor outcomes between the two DBS targets.

A recent trial conducted by the St. Jude Medical DBS Study Group [26] assessed the safety and efficacy of constant-current DBS after implantation into the STN. The study provided a novel look at the effects of device implantation alone (without activation) by randomizing PD patients to immediate versus 3-month-delayed (25% of patients) activation of DBS. Although both groups reported a mean increase in quality on time after 3 months, the improvement was greater in the stimulation group. Follow-up after 3 months of DBS surgery revealed that the on time had improved on average by almost 2 h in the nonstimulated group, confirming the clinical effect of lead implantation alone (e.g. microlesional effect) as an important factor for consideration among physicians.

In recent years, there has been interest in studying the effects of DBS in earlier PD stages though there is great controversy with regard to how to define early PD [11]. The EARLYSTIM Study [27] was a 2-year trial of PD patients with 7.3 years (± 3.1) of disease duration and with

very early motor complications (mean duration: dyskinesia 1.4 ± 0.8 years and motor fluctuation 1.6 ± 0.8 years) who underwent bilateral STN DBS plus best medical therapy, or alternatively just best medical therapy. For the primary outcome of change in PDQ-39 quality of life, the mean score for the neurostimulation group improved by 7.8 points (26%) versus that of the medical therapy group, which worsened by 0.2 points (1%). These results suggested that STN DBS was superior to medical therapy in patients with PD and early motor complications. The study, however, notably enrolled only young patients with an average age of 52.9 years (± 6.6), and therefore it is unclear how these findings will generalize to older populations, especially those in their 60s and 70s.

Vanderbilt University is currently conducting a prospective, randomized, single-blind clinical trial of optimal drug therapy (ODT) compared to medication plus DBS (ODT + DBS) in subjects with early-stage idiopathic PD without motor fluctuations or dementia. The results have yet to be published [28].

Collectively, the results of these randomized DBS studies suggest that in well-selected patient, all of whom have undergone a multi- or interdisciplinary evaluation, DBS may be superior to best medical management. Table 2 summarizes the major published DBS studies.

What Is the Evidence Supporting the Use of DBS in ET?

No controlled trials of DBS have been done in ET, but two prospective, class III trials have examined the effects of DBS. Although the treatment was not randomized, evaluation was conducted in a blinded and random manner [29, 30].

In the North American Multi-Center Trial, 25 ET patients and 24 PD patients were followed for 1 year after implantation. Combined blinded tremor ratings (0–4) in ET patients randomized to 'on' were 0.9 compared to 2.7 for those randomized to 'off' stimulation. All subjective functional measures improved, and 9 of 29 patients (31%) had complete tremor cessation [31]. In the second trial, 9 ET patients with disabling tremor refractory to pharmacotherapy underwent bilateral staged implants and there was a significant improvement in the mean total tremor score from a baseline of 66.1 ± 11.6 to 28.4 ± 12.8 at 12 months after the second surgery [32].

Several studies have demonstrated the efficacy of thalamic DBS in ET after 1–2 years of treatment. A large

Table 2. PD DBS randomized clinical trials

Patient characteristics	German Study Group [19]	PD SURG Collaborative Group [20]	CSP 468 Study Group [21]	NIH COMPARE Study [25]	St. Jude Medical DBS Study Group [26]	EARLYSTIM Study [27]
Age, years	60.5±7.4	59 (range 37–79)	62.4±8.8 (>70.25)	60.0±8.2	60.8±8.3	52.9±6.6
Male sex, n (%)	50 (64)	125 (68)	98 (81)	67.3%	63 (62)	94 (75.8)
Disease duration, years	–	11.5	12.4±5.8	12.9±3.8	12.1±4.9	7.3±3.1
LD treatment duration, years	13±5.8	–	10.8±5.4	–	–	4.8±3.3
LEDD, mg/day	1,175±517	–	–	1,054.9±517.1	1,311±615	918.8±412.5
HY, n (%)			3.4±0.9		2.94±0.80	–
≤2	1 (1)	12 (7)		16.3%		
2.5	10 (13)	19 (11)		18.4%		
3	17 (22)	65 (38)		51%		
4	40 (51)	54 (32)		12.2%		
5	10 (13)	19 (11)		2%		
Medical treatment	According to local practice	According to local practice	According to local practice	–	–	According to local practice
Surgery	Bilateral STN	STN/Gpi; stimulation/lesion	Bilateral STN/Gpi	Unilateral STN/Gpi	Bilateral STN	Bilateral STN
Targeting technique	Varying depending on the center	Varying depending on the center	MER was used	MER was used	MER was used	MER was used
Primary outcome	PDQ-39 UPDRS-III	PDQ-39	On state without troubling dyskinesia	Mood and cognitive function	On time without dyskinesia or nonbother-some dyskinesia	PDQ-39
Results	PDQ-39 25% and UPDRS-III 48% improvement in the DBS group	–4.7 points of difference in improvement	4.6 vs. 0 h/day in the DBS group	No differences; when stimulation was shifted within targets more verbal fluency deficits in STN were found	73.3 vs. 38.2% responder rate; 3-month microlesional effect	26 vs. –1% improvement

LD = Levodopa; LEDD = levodopa equivalent daily dosage; HY = Hoehn and Yahr; MER = microelectrode recording.

North American study showed that there was no loss of effect after 1 year [31]. Similarly, the experience in the European multicenter study found that the effectiveness was maintained over the first several years [33]. The long-term (5- to 10-year) efficacy of thalamic DBS is presently not well established, but several studies now report positive improvements 10 years after implantation. Preliminary information suggests a maintained (mean 60%) improvement in tremor, with a mild trend toward a reduction in efficacy as the time after surgery increases [34]. This slow worsening of tremor has been hypothesized to be disease progression and not tolerance. Prospective trials to evaluate the long-term efficacy of DBS in ET are needed.

What Is the Importance of a Multi- or Interdisciplinary DBS Team for Patient Selection?

Performance of a complete multi- or interdisciplinary preoperative DBS assessment prior to consideration of DBS surgery has been recommended [35]. The primary care doctor should refer potential DBS candidates to experienced teams. It is important to keep in mind that most patients with PD and ET around the world are followed not by neurologists but by primary care doctors, thus emphasizing the importance of the primary care doctor in facilitating DBS operations. These teams include a neurologist, a neurosurgeon, a psychologist, a psychiatrist, therapists (physical, occupational, speech),

Fig. 1. ‘Fast-track’ workup pathway of the University of Florida. OT = Occupational therapy; PT = physical therapy; SCID = severe combined immunodeficiency; TRS = tremor rating scale; UDRS =

unified dystonia rating scale; BFMDRS = Burke-Fahn-Marsden dystonia rating scale; TWSRTS = Toronto western spasmodic torticollis rating scale.

and possibly other members of a health care team. Each member of the screening team should individually assess the patient and, if not done concurrently (in real-time, interdisciplinary), a meeting should be organized to review, discuss findings, and recommend/reject DBS surgery. Patients moving forward with surgery will require a thorough discussion of the surgical approach and brain target(s), as well as coordinated postoperative care. Issues such as cognitive impairment or active psychiatric disease, as well as patient expectations, commonly drive the discussion among DBS multidisciplinary teams.

Once an evaluation and discussion have been completed, the patient should be contacted and apprised of the interdisciplinary discussion(s) and informed of the risks and benefits and whether the surgery will possibly meet their preoperative expectations for potential benefit. Figure 1 summarizes the interdisciplinary University of Flor-

ida ‘fast-track’ process, as well as the details of the follow-up interdisciplinary discussion. ‘Fast track’ was a term coined at the University of Florida to refer to a process whereby patients can be evaluated by multiple multidisciplinary specialties on consecutive days. Each fast-track work-up is followed by a multidisciplinary discussion. Not all DBS centers have psychiatrists on their teams, and in cases where a psychiatrist is not available screening is usually performed by a neuropsychologist. In our experience, we have found the psychiatrist and the psychiatry evaluation to be important, and we would encourage centers without this expertise to refer cases for specialty care if any psychiatric issues emerge during the screening process. Overall, the role of the interdisciplinary team is to provide a tailored approach for each potential DBS candidate that will ultimately maximize the risk-benefit ratio and minimize potential DBS failures [11].

Post-Op Process: Brief Summary

Optimization of Settings

Stimulation through the inserted lead is typically delayed for a few weeks following surgical implantation to allow for the resolution of brain edema around the inserted DBS lead. The pulse generator settings that are used for DBS in both ET and PD are typically high frequency (130–185 Hz), with pulse widths of 60–120 μ s at voltages ranging from 2.0 to 5.0 V. Such settings can be highly variable among patients, and frequent adjustment of the stimulation settings is necessary during the first few months following implantation in order to ensure optimization. Optimization also involves medication adjustments, and notably not all cases of DBS will result in medication reduction [6].

Causes of Treatment Failure: DBS Failures

In a study of patients with a suboptimal response to DBS, common causes observed included deficiencies in patient selection and screening, suboptimal lead positioning, insufficient attention to device programming, and inadequate medication adjustment. Most of these issues could be avoided with careful screening and follow-up. Occasionally, some DBS patients benefited from the addition of a rescue lead (a lead placed in the same brain target or another target to enhance benefit), particularly if the original DBS lead was providing some benefit. Some DBS patients, however, required complete lead replacement. Troubleshooting is therefore a critical aspect of the long-term management of DBS and has the potential to enhance outcomes [36].

What Can Be Done to Improve Success in Identifying and Referring Potential DBS Candidates?

Since DBS in the ‘right’ patients commonly results in a marked reduction in disability, and an often dramatic improvement in quality of life, selection has become the most critical step in the procedure. Since many more patients are undergoing DBS (>100,000 currently with brain DBS devices manufactured by Medtronic, Minneapolis, Minn., USA), and most are diagnosed and subsequently followed by primary care physicians, it will be critical for clinicians in primary care settings to learn to recognize potential DBS candidates. Identifying patients who are likely to benefit from DBS will be the important first step toward a successful surgical intervention and ultimate postoperative course [37]. More than 30% of DBS failures

in a previous study were ascribed to inappropriate patient selection, so education of primary physicians will be extremely important [36].

Although screening tools have been developed for appropriate patient selection for PD surgery, such as the CAPSIT-PD [38], there is still no standardized assessment tool. An electronic decision tool (RAND/UCLA method) [39] that can assist neurologists in deciding which PD patients should be referred for DBS evaluation was recently developed. Using this method, 33% of the theoretical profiles were considered appropriate. Symptom severity and PD duration were positively associated with a better outcome, while levodopa-resistant axial symptoms, age more than 70 years, and presence of cognitive impairment were negatively associated with outcome as judged by an expert panel. No tool has been universally adopted in DBS therapy.

In an effort to improve DBS surgical referral patterns from primary doctors, a screening tool was recently developed and validated, i.e. the Florida Surgical Questionnaire for Parkinson Disease (FLASQ-PD) [40]. The FLASQ-PD is a 5-section questionnaire. The scoring system was designed to assign higher scores to better surgical candidates. The highest/best possible score was 34 with 0 ‘red flags’, and the lowest/worse possible score was 0 with 8 red flags. A red flag was a sign or symptom that would place a patient at high risk for a DBS complication. A score of approximately 25 without red flags indicates a potentially good candidate. The questionnaire could be filled out and scored by a primary care physician or general neurologist. We recommend that potential candidates identified by this method be referred to an expert DBS center for further multi- or interdisciplinary evaluation.

Although there are no standardized criteria for surgical candidacy, the best overall results have been reported in patients with advanced PD, those with an excellent response to levodopa (greater than 30% improvement when in their on medication state), younger age candidates, candidates with no or few axial non-LD responsive motor symptoms (e.g. walking, talking, and thinking), candidates with no or very mild cognitive impairment, and candidates with an absence of or alternatively those with well-controlled psychiatric disease [41].

Review of the FLASQ-PD subscales can provide information on patient selection issues in DBS surgery.

Criteria for the Diagnosis of ‘Probable’ Idiopathic PD

Patients must meet the diagnosis for ‘probable’ idiopathic PD [14]. Diagnosis is contingent on the following:

- presence of bradykinesia;

- presence of at least 1 of the following: muscular rigidity, 4- to 6-Hz rest tremor, and postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction;
- 3 or more of the following: unilateral onset, rest tremor or present, progressive disorder, persistent asymmetry mostly affecting the side of onset, excellent response (70–100%) to levodopa, severe levodopa-induced chorea, levodopa response for 5 years or more, and a clinical course of 10 years or more.

Potential Contraindications for PD Surgery

Red flags are a collection of signs and symptoms that may represent contraindications to surgery (table 3).

General Patient Characteristics

Several general characteristics, if present, will improve surgical candidacy. No specific age cutoff has been defined in clinical DBS studies. The major concerns with age have been associated comorbidities, cognitive decline, a higher incidence of LD-resistant symptoms, and a higher overall risk of surgical complications [42].

Operating on patients earlier than 5 years following a PD diagnosis could lead to the inclusion of patients with atypical parkinsonism. For that reason, a general criterion has been to choose patients with at least 5 years of diagnosis. In addition, it is a reasonable amount of time to attempt to treat the patient with medications before considering a surgical intervention.

Surgery has been mainly directed at treating motor disability. The disability can be related to motor fluctuations, dyskinesias, or dystonia. These symptoms typically respond well to DBS. Recent guidelines consider both STN and GPi DBS efficacious for the treatment of dyskinesia and motor fluctuations. Additionally, DBS surgery is excellent at addressing medication-resistant tremor and in enhancing the number of hours of quality on time for a sufferer [43, 44].

Favorable/Unfavorable Characteristics

In PD, the symptoms that improve with levodopa are generally the symptoms that will improve with surgery, with the exception of medication-refractory tremor. Problems such as postural instability, gait, balance, and particularly freezing will typically not improve with DBS. Some patients will experience improvement in these symptoms; however, with progression of PD, they will likely reemerge. It is important for patients to be aware of this issue. The University of Florida mnemonic [45] for patients with PD considering DBS is shown in table 4.

Table 3. Red flags in evaluation of parkinsonism

Motor

Rapid progression
Instability and early falls
Early freezing
Poor response to levodopa
Stimulus-sensitive myoclonus
Oro-facial dystonia
Camptocormia
Pisa syndrome
Antecollis
Rocket sign
Procerus sign
Pyramidal signs
Cerebellar signs
Early bulbar symptoms
Contractures
Dystonias
Axial rigidity

Autonomic

Erectile dysfunction
Early urinary incontinence, frequency, urgency
Fecal incontinence
Progressive anhidrosis
Nocturnal stridor
Cold hands/feet sign

Oculomotor

Slow vertical saccades
Difficulty initiating saccades
Supranuclear gaze palsy
Square-wave jerks
Downbeat gaze-evoked and positional nystagmus

Cortical

Early and severe frontal dementia
Visual hallucinations
Ideomotor apraxia
Primary progressive aphasia
Cortical sensory loss
Visual/sensitive negligence

Several other useful characteristics should be considered when choosing DBS candidates. PD patients treated with anticoagulants, those with swallowing dysfunction, and those with difficult to address comorbidities (severe hypertension, diabetes, incontinence) that have the potential to worsen following surgery should be approached cautiously. Frank dementia is the most frequent reason for a DBS interdisciplinary team to deny surgery. Additionally, surgery is generally deferred in patients with unstable affective or psychiatric conditions until their symptoms have been adequately managed [46].

Table 4. University of Florida mnemonic device for patients with PD considering DBS (DBS in PD)

Does not cure
Bilateral DBS is often required to improve gait, although sometimes unilateral DBS has a marked effect on walking
Smooth out on/off fluctuations
Improves tremor, bradykinesia (slowness), stiffness (rigidity), and dyskinesia in most cases, but may not completely eliminate them
Never improves symptoms that are unresponsive to your best 'on'; for example, if gait or balance does not improve with the 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 follow-up visits occur 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

Table 5. Red flags in the evaluation of tremors

Red flags	Differential diagnosis
Unilateral tremor, rest tremor, re-emergent tremor, rigidity, bradykinesia	PD
Gait disturbances	PD, cerebellar tremor
Focal tremor, isolated head tremor with abnormal posture, tremor increases when turning the head	Dystonic tremor
Sudden or rapid onset, inconsistent during examination	Psychogenic or toxic tremor
Current drug treatment that might cause or exacerbate tremor	Drug-induced or toxic tremor

Medication Trial

Levodopa responsiveness has been universally accepted as the single best predictor of outcome for DBS response [37]. Prior to referring a patient for DBS surgery, the primary care doctor should consider whether there has been an adequate medication trial. Since PD medications can be very complex to manage, primary care doctors should have a low threshold for referral for work-up by an expert DBS center, as medication optimization can occur in that setting.

Many neurologists use the UPDRS when patients are in their 'off medication' state, following a period of 12 h without medications (usually overnight). Patients are then administered a supratherapeutic dose of their medications (given an extra half or 1 tablet of carbidopa/levodopa), and then repeat motor testing (UPDRS part III) is performed. In general, the best surgical candidates experience a change of at least 30% on this scale. Exceptions to this rule should be considered on a case-by-case basis and include patients with severe tremor resistance and those with severe or violent dyskinesias. As DBS has evolved as a therapy, many multi- interdisciplinary teams now consider some nonideal candidates (exceptional or palliative cases).

In ET, the appropriate selection of patients is critical for the outcome and surgical relief of symptoms. No screening tools have been developed for appropriate patient selection for surgery in ET; however, the same interdisciplinary workup is necessary. We suggest primary care doctors select potential candidates for DBS based on the following factors [47].

Confirm the Diagnosis

Distinguish ET from other causes of tremors (PD, cerebellar, multiple sclerosis, dystonic tremor, Holmes tremor, peripheral neuropathy, drug-induced tremors, psychogenic disorders). Table 5 provides red flags indicating tremor disorders other than ET.

Assess the Patient's Disability

Patients must have medication-refractory tremor (defined as having failed maximal titrations and preferably combinations of a beta-blocker, primidone, and possibly a benzodiazepine, and other medications may have been tried as well). The tremor must be interfering with the quality of life (feeding, drinking, dressing, and writing).

Discuss Expectations

It is accepted that ET is a slowly progressive disease, and as the disease advances the frequency of the tremor may decrease and the amplitude increases, usually resulting in more disability over many years.

What Are the Chances for Medical Treatment in a Particular Patient?

In general, the less pronounced the symptoms, the better the chances of a favorable outcome with medical treatment. In other words, the more severe the symptoms are, the less likely medication will help.

Outcome of Surgery

Rest, postural, and action tremor are likely to respond to DBS, but action tremor is the most difficult to completely capture. Proximal tremor (shoulder involvement) is less responsive.

Evaluate for Individual Risks of Complications

Consider any other medical comorbidity, age, or any life-limiting disease. Also dementia or severe brain atrophy are risks that threaten a good outcome.

Conclusion

DBS can be a highly effective therapy for well-selected PD and ET patients. Selection of the appropriate candidates for surgery is the most important factor impacting the DBS outcome. It is critical for primary care physicians to learn to select candidates, and to refer potential PD and ET candidates to specialized centers.

References

- 1 Scribonius L, Helmreich G: Compositiones. Leipzig, Teubner, 1887, vii, 1, 123, 121 p.
- 2 Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J: Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl Neurophysiol* 1987;50:344–346.
- 3 Hariz M: Twenty-five years of deep brain stimulation: celebrations and apprehensions. *Mov Disord* 2012;27:930–933.
- 4 Miocinovic S, Somayajula S, Chitnis S, Vitek JL: History, applications, and mechanisms of deep brain stimulation. *JAMA Neurol* 2013; 70:163–171.
- 5 Rascol O, Lozano A, Stern M, Poewe W: Milestones in Parkinson's disease therapeutics. *Mov Disord* 2011;26:1072–1082.
- 6 Okun MS: Deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2012;367: 1529–1538.
- 7 Vitek JL: Mechanisms of deep brain stimulation: excitation or inhibition. *Mov Disord* 2002;17(suppl 3):S69–S72.
- 8 Vedam-Mai V, van Battum EY, Kamphuis W, Feenstra MG, Denys D, Reynolds BA, Okun MS, Hol EM: Deep brain stimulation and the role of astrocytes. *Mol Psychiatry* 2012;17: 115, 124–131.
- 9 Tawfik VL, Chang SY, Hitti FL, Roberts DW, Leiter JC, Jovanovic S, Lee KH: Deep brain stimulation results in local glutamate and adenosine release: investigation into the role of astrocytes. *Neurosurgery* 2010;67:367–375.
- 10 Lee KH, Chang SY, Roberts DW, Kim U: Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. *J Neurosurg* 2004;101:511–517.
- 11 Okun MS, Foote KD: Parkinson's disease DBS: what, when, who and why? The time has come to tailor DBS targets. *Expert Rev Neurother* 2010;10:1847–1857.
- 12 Rodriguez RL, Fernandez HH, Haq I, Okun MS: Pearls in patient selection for deep brain stimulation. *Neurologist* 2007;13:253–260.
- 13 Jankovic J: Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry* 2008;79:368–376.
- 14 Hughes AJ, Daniel SE, Kilford L, Lees AJ: Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–184.
- 15 Chaudhuri KR, Schapira AH: Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. *Lancet Neurol* 2009;8:464–474.
- 16 Louis ED, Okun MS: It is time to remove the 'benign' from the essential tremor label. *Parkinsonism Relat Disord* 2011;17:516–520.
- 17 Deuschl G, Bain P, Brin M: Consensus statement of the Movement Disorder Society on Tremor – ad hoc Scientific Committee. *Mov Disord* 1998;13(suppl 3):2–23.
- 18 Chandran V, Pal PK: Essential tremor: beyond the motor features. *Parkinsonism Relat Disord* 2012;18:407–413.
- 19 Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schafer H, Botzel K, Daniels C, Deutschlander A, Dillmann U, Eisner W, Gruber D, Hamel W, Herzog J, Hilker R, Klebe S, Kloss M, Koy J, Krause M, Kupsch A, Lorenz D, Lorenz S, Mehdorn HM, Moringlane JR, Oertel W, Pinski MO, Reichmann H, Reuss A, Schneider GH, Schnitzler A, Steude U, Sturm V, Timmermann L, Tronnier V, Trottenberg T, Wojtecki L, Wolf E, Poewe W, Voges J, German Parkinson Study Group, Neurostimulation Section: A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;355: 896–908.
- 20 Williams A, Gill S, Varma T, Jenkinson C, Quinn N, Mitchell R, Scott R, Ives N, Rick C, Daniels J, Patel S, Wheatley K, PD Surg Collaborative Group: Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol* 2010;9:581–591.
- 21 Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ Jr, Rothlind J, Sagher O, Reda D, Moy CS, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein J, Stoner G, Heemskerk J, Huang GD, CSPPS 468 Study Group: Bilateral deep brain stimulation vs. best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 2009;301: 63–73.
- 22 Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, Marks WJ Jr, Rothlind J, Sagher O, Moy C, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein JM, Stoner G, Starr PA, Simpson R, Baltuch G, De Salles A, Huang GD, Reda DJ, CSP 468 Study Group: Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2010;362:2077–2091.
- 23 Weaver FM, Follett KA, Stern M, Luo P, Harris CL, Hur K, Marks WJ Jr, Rothlind J, Sagher O, Moy C, Pahwa R, Burchiel K, Hogarth P, Lai EC, Duda JE, Holloway K, Samii A, Horn S, Bronstein JM, Stoner G, Starr PA, Simpson R, Baltuch G, De Salles A, Huang GD, Reda DJ, CSPPS 468 Study Group: Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology* 2012;79:55–65.
- 24 Anderson VC, Burchiel KJ, Hogarth P, Favre J, Hammerstad JP: Pallidal vs. subthalamic nucleus deep brain stimulation in Parkinson disease. *Arch Neurol* 2005;62:554–560.
- 25 Okun MS, Fernandez HH, Wu SS, Kirsch-Darrow L, Bowers D, Bova F, Suelter M, Jacobson CE 4th, Wang X, Gordon CW Jr, Zeilman P, Romrell J, Martin P, Ward H, Rodriguez RL, Foote KD: Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. *Ann Neurol* 2009;65:586–595.
- 26 Okun MS, Gallo BV, Mandybur G, Jagid J, Foote KD, Revilla FJ, Alterman R, Jankovic J, Simpson R, Junn F, Verhagen L, Arle JE, Ford B, Goodman RR, Stewart RM, Horn S, Baltuch GH, Kopell BH, Marshall F, Peichel D, Pahwa R, Lyons KE, Troster AI, Vitek JL, Tagliati M, SJM DBS Study Group: Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurol* 2012;11:140–149.

- 27 Schuepbach WM, Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, Halbig TD, Hessekamp H, Navarro SM, Meier N, Falk D, Mehdorn M, Paschen S, Maarouf M, Barbe MT, Fink GR, Kupsch A, Gruber D, Schneider GH, Seigneuret E, Kistner A, Chaynes P, Ory-Magne F, Brefel Courbon C, Vesper J, Schnitzler A, Wojtecki L, Houeto JL, Bataille B, Maltete D, Damier P, Raoul S, Sixel-Doering F, Hellwig D, Gharabaghi A, Kruger R, Pinsker MO, Amtege F, Regis JM, Witjas T, Thobois S, Mertens P, Kloss M, Hartmann A, Oertel WH, Post B, Speelman H, Agid Y, Schade-Brittinger C, Deuschl G, EARLYSTIM Study Group, ES: Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med* 2013;368:610–622.
- 28 Charles PD, Dolhun RM, Gill CE, Davis TL, Bliton MJ, Tramontana MG, Salomon RM, Wang L, Hedera P, Phibbs FT, Neimat JS, Konrad PE: Deep brain stimulation in early Parkinson's disease: enrollment experience from a pilot trial. *Parkinsonism Relat Disord* 2012;18:268–273.
- 29 Zesiewicz TA, Elble R, Louis ED, Hauser RA, Sullivan KL, Dewey RB Jr, Ondo WG, Gronseth GS, Weiner WJ, Quality Standards Subcommittee of the American Academy of Neurology: Practice parameter: therapies for essential tremor – report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2005;64:2008–2020.
- 30 Zesiewicz TA, Elble RJ, Louis ED, Gronseth GS, Ondo WG, Dewey RB Jr, Okun MS, Sullivan KL, Weiner WJ: Evidence-based guideline update: treatment of essential tremor – report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2011;77:1752–1755.
- 31 Koller W, Pahwa R, Busenbark K, Hubble J, Wilkinson S, Lang A, Tuite P, Sime E, Lazano A, Hauser R, Malapira T, Smith D, Tarsy D, Miyawaki E, Norregaard T, Kormos T, Olanow CW: High-frequency unilateral thalamic stimulation in the treatment of essential and parkinsonian tremor. *Ann Neurol* 1997;42:292–299.
- 32 Pahwa R, Lyons KL, Wilkinson SB, Carpenter MA, Troster AI, Searl JP, Overman J, Pickering S, Koller WC: Bilateral thalamic stimulation for the treatment of essential tremor. *Neurology* 1999;53:1447–1450.
- 33 Sydow O, Thobois S, Alesch F, Speelman JD: Multicentre European study of thalamic stimulation in essential tremor: a six year follow up. *J Neurol Neurosurg Psychiatry* 2003;74:1387–1391.
- 34 Rehnacrona S, Johnels B, Widner H, Tornqvist AL, Hariz M, Sydow O: Long-term efficacy of thalamic deep brain stimulation for tremor: double-blind assessments. *Mov Disord* 2003;18:163–170.
- 35 Houeto JL, Damier P, Bejjani PB, Staedler C, Bonnet AM, Arnulf I, Pidoux B, Dormont D, Cornu P, Agid Y: Subthalamic stimulation in Parkinson disease: a multidisciplinary approach. *Arch Neurol* 2000;57:461–465.
- 36 Okun MS, Tagliati M, Pourfar M, Fernandez HH, Rodriguez RL, Alterman RL, Foote KD: Management of referred deep brain stimulation failures: a retrospective analysis from 2 movement disorders centers. *Arch Neurol* 2005;62:1250–1255.
- 37 Lang AE, Houeto JL, Krack P, Kubu C, Lyons KE, Moro E, Ondo W, Pahwa R, Poewe W, Troster AI, Uitti R, Voon V: Deep brain stimulation: preoperative issues. *Mov Disord* 2006;21(suppl 14):S171–S196.
- 38 Defer GL, Widner H, Marie RM, Remy P, Levivier M: Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord* 1999;14:572–584.
- 39 Moro E, Allert N, Eleopra R, Houeto JL, Phan TM, Stoevelaar H, International Study Group on Referral Criteria for DBS: A decision tool to support appropriate referral for deep brain stimulation in Parkinson's disease. *J Neurol* 2009;256:83–88.
- 40 Okun MS, Fernandez HH, Pedraza O, Misra M, Lyons KE, Pahwa R, Tarsy D, Scollins L, Corapi K, Friehs GM, Grace J, Romrell J, Foote KD: Development and initial validation of a screening tool for Parkinson disease surgical candidates. *Neurology* 2004;63:161–163.
- 41 Bronstein JM, Tagliati M, Alterman RL, Lozano AM, Volkmann J, Stefani A, Horak FB, Okun MS, Foote KD, Krack P, Pahwa R, Henderson JM, Hariz MI, Bakay RA, Rezai A, Marks WJ Jr, Moro E, Vitek JL, Weaver FM, Gross RE, DeLong, MR: Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. *Arch Neurol* 2011;68:165.
- 42 Derost PP, Ouchchane L, Morand D, Ulla M, Llorca PM, Barget M, Debilly B, Lemaire JJ, Durif F: Is DBS-STN appropriate to treat severe Parkinson disease in an elderly population? *Neurology* 2007;68:1345–1355.
- 43 Pahwa R, Factor SA, Lyons KE, Ondo WG, Gronseth G, Bronte-Stewart H, Hallett M, Miyasaki J, Stevens J, Weiner WJ, Quality Standards Subcommittee of the American Academy of Neurology: Practice parameter: treatment of Parkinson disease with motor fluctuations and dyskinesia (an evidence-based review) – report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006;66:983–995.
- 44 Fox SH, Katzenschlager R, Lim SY, Ravina B, Seppi K, Coelho M, Poewe W, Rascol O, Goetz CG, Sampaio C: The Movement Disorder Society evidence-based medicine review update: treatments for the motor symptoms of Parkinson's disease. *Mov Disord* 2011;26(suppl 3):S2–S41.
- 45 Okun MS, Foote KD: A mnemonic for Parkinson disease patients considering DBS: a tool to improve perceived outcome of surgery. *Neurologist* 2004;10:290.
- 46 Okun MS, Fernandez HH, Rodriguez RL, Foote KD: Identifying candidates for deep brain stimulation in Parkinson's disease: the role of the primary care physician. *Geriatrics* 2007;62:18–24.
- 47 Deuschl G, Bain P: Deep brain stimulation for tremor (correction of trauma): patient selection and evaluation. *Mov Disord* 2002;17(suppl 3):S102–S111.