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REVIEW

Surgical Treatment of Parkinson's Disease: Devices and Lesion Approaches

Vibhash D. Sharma[1] · Margi Patel[2] · Svjetlana Miocinovic[2]

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Abstract
Surgical treatments have transformed the management of Parkinson's disease (PD). Therapeutic options available for the management of PD motor complications include deep brain stimulation (DBS), ablative or lesioning procedures (pallidotomy, thalamotomy, subthalamotomy), and dopaminergic medication infusion devices. The decision to pursue these advanced treatment options is typically done by a multidisciplinary team by considering factors such as the patient's clinical characteristics, efficacy, ease of use, and risks of therapy with a goal to improve PD symptoms and quality of life. DBS has become the most widely used surgical therapy, although there is a re-emergence of interest in ablative procedures with the introduction of MR-guided focused ultrasound. In this article, we review DBS and lesioning procedures for PD, including indications, selection process, and management strategies.

Key Words Deep brain stimulation · ablation · RF ablation · stereotactic radiosurgery · focused ultrasound

When to Consider Surgical Therapies in Parkinson's Disease

Oral medications, including dopaminergic and nondopaminergic options, are the mainstay of management in Parkinson's disease (PD). Early in the disease course, medical management is effective in controlling motor symptoms and improving quality of life in a majority of patients. However, with disease progression and chronic use of dopaminergic therapies, patients can develop motor fluctuations (off periods, dose failures) and dyskinesia. For some patients, even early in the disease course, medication side effects can limit their therapeutic effectiveness, or tremor may be medication refractory. Surgical and other advanced treatment options should therefore be considered for patients whose symptoms cannot be adequately managed by oral medications alone. Prior to considering such advanced therapies, generally, the dose and frequency of dopaminergic medications should be optimized.

✉ Vibhash D. Sharma
vsharma3@kumc.edu

[1] Department of Neurology, University of Kansas Medical Center, 3599 Rainbow Blvd, MS 3042, Kansas City, KS 66160, USA

[2] Department of Neurology, Emory University, Atlanta, GA, USA

The currently available advanced treatments include deep brain stimulation (DBS), ablative or lesioning procedures, and dopaminergic medication infusion devices (Fig. 1). These therapies have one of the following two effects: improvement of motor symptoms through targeted stimulation/ablation of the motor circuit and continuous dopaminergic medication delivery. The decision to pursue advanced therapies is typically guided by unsatisfactory control of motor symptoms, although both positive and negative effects on non-motor symptoms may often be observed.

Because there is no evidence to date that these therapies are disease modifying, the decision to pursue advanced treatments depends largely on the patient's satisfaction with his or her symptom control and ability to carry out desired activities. In addition to medical appropriateness, which is discussed in detail in following sections, the choice of advanced therapy and its timing should also be guided by the patient's priorities and expectations (which need to be adequately addressed), personal tolerance to risk, and ability to comply with therapy requirements (e.g., clinic visits, device management). Advanced therapies should not be viewed as the last resort reserved for patients with late-stage disease. The term "window of opportunity" is sometimes used in reference to DBS surgery to indicate that it should be offered/pursued while the patient can functionally benefit from the procedure; similarly, this concept is applicable to lesioning procedures. Lack of

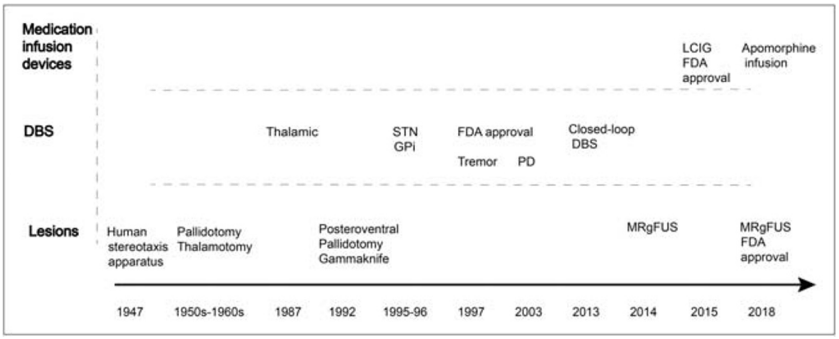

Fig. 1 Evolution of surgical treatments in PD over time. DBS = deep brain stimulation, STN = subthalamic nucleus, GPi = globus pallidus interna, FDA = Food and Drug Administration, LCIG = levodopa carbidopa intestinal gel, MRgFUS = MR-guided focused ultrasound

accurate information can make a patient either unnecessarily fearful or inappropriately enthusiastic. Therefore, a comprehensive and timely discussion of advanced therapy options should be available to all patients with PD.

Multidisciplinary Presurgical Evaluation

Several factors are taken into consideration to determine the appropriateness and to optimize the outcome of a surgical therapy in patients with PD. A careful presurgical evaluation by a multidisciplinary team is recommended to assess candidacy as different motor symptoms may have varying response to the surgical therapy. A multidisciplinary team typically consists of a movement disorders neurologist, a neurosurgeon, a neuropsychologist, a psychiatrist/psychologist, and allied health professionals (physical, speech, and/or occupational therapists). As some neurology practices may not have a multidisciplinary team for surgical evaluation, the primary neurologist should refer potential surgical candidates to a center with expertise in these procedures. An initial consultation with a movement disorders neurologist can be particularly helpful to 1) confirm the diagnosis, 2) review the appropriateness of oral medication trials, and 3) assess motor and non-motor symptoms and their potential responsiveness to advanced therapy options. Important issues to address prior to the surgery include patient and family expectations, and a detailed discussion of potential risks and benefits of the surgical procedure. This should be followed by comprehensive evaluation by other team members. Different factors are assessed including neurocognitive and psychiatric profile, neuroimaging, on–off levodopa challenge, surgical risks, and current level of function. After evaluations are completed, team members meet in an interdisciplinary conference to review patient factors to determine which surgical therapy is appropriate for the patient and details including the brain target, bilateral *versus* unilateral procedure, staged *versus* simultaneous, and type of surgical technique (e.g., awake *vs* asleep, type of lesioning procedure, etc.) are discussed. Availability of social and clinical support postsurgery should also be taken into consideration. Any issues or concerns related to the patient and surgery should be discussed and addressed prior to the surgical therapy. Some patients may not be considered for surgical therapy after comprehensive evaluation; in those cases, alternative options for management and improving quality of life should be discussed.

Deep Brain Stimulation

DBS therapy involves modulation of neural networks with electric currents delivered through surgically implanted electrodes connected to a neurostimulator. Since the introduction of levodopa, DBS therapy is considered as the second most important breakthrough for PD treatment.

Introduction of the human stereotaxis apparatus by Wycis and Spiegel in 1947 marked the beginning of closed stereotactic neurosurgery [1]. Subsequently, during the 1950s, stereotactic atlases were introduced and there was an increase in stereotactic surgery research [2, 3]. During this time, Irving Cooper made a serendipitous observation that pallidal infarct due to ligation of the anterior choroidal artery alleviates parkinsonian symptoms, which further emphasized the role of basal ganglia in motor control [4]. Consequently, surgical management of PD was focused on thalamotomy and pallidotomy surgeries [2, 5]. Intraoperative electrical stimulation was used during ablative surgeries to aid in target localization. Although observations that thalamic stimulation can cause tremor suppression were reported, these findings were not well defined [6, 7]. With the discovery of levodopa [8], surgical therapies declined significantly during the the 1960s and 1970s. However, the long-term motor complications soon became apparent and interest in surgical therapies was regained [9, 10]. In the 1980s, physiological studies in animal models expanded the understanding of basal ganglia pathways and the pathophysiology of PD [11, 12].

In 1987, Benabid and colleagues [13] reported reversible suppression of tremor with high-frequency thalamic electrical stimulation. This procedure offered a reversible and adjustable approach for controlling tremor compared to lesioning, and eventually, DBS was approved by the Food and Drug

Administration (FDA) for unilateral PD tremor and essential tremor (ET) in 1997 [14, 15]. Following this development, based on previous experience with pallidotomy and the observation of marked improvement in parkinsonism with subthalamic nucleus (STN) lesions in primates [16, 17], high-frequency stimulation in the globus pallidus pars interna (GPi) and STN was performed [18, 19] and, after the results of clinical trials, DBS therapy for PD was approved by the FDA in 2003. The field of DBS is constantly evolving with an advancement in the understanding of neural mechanisms, innovation in technology, and development of next-generation DBS devices.

Patient Selection

Clinical outcomes of DBS therapy depend on patient selection, accurate lead placement in the therapeutic target, postoperative DBS programming, and medication adjustment. Careful selection of appropriate candidates is crucial for favorable outcomes as DBS is not beneficial for all patients with PD. It is estimated that 30% of unfavorable DBS outcomes could be related to inappropriate patient selection [20]. Patients with a diagnosis of idiopathic PD with levodopa-induced motor complications or medication refractory tremor with no symptoms/signs concerning for atypical parkinsonism (early postural instability, supranuclear gaze palsy, severe early dysautonomia) are ideal candidates for DBS therapy. Patients with postural instability, uncontrolled neuropsychiatric issues, and multiple comorbidities may be poor candidates. Dementia and atypical parkinsonism are contraindications for DBS surgery; however, further studies are needed to see whether patients with mild dementia and severe motor complications could benefit from DBS surgery. Levodopa responsiveness should be assessed during on–off testing as it is an important predictor of good clinical outcomes. On the contrary, poor levodopa response or presence of axial features during "on period" may predict worse outcomes [21, 22]. Neuropsychological cognitive evaluation is typically performed to assess cognitive function and mood state, both of which could be used to determine patient candidacy and target choice.

Optimal age for DBS surgery is not well established, with some studies suggesting younger age is a predictor of favorable motor outcomes [22, 23], whereas other studies did not support these findings [24–26]. Although there is no defined age limit for DBS surgeries, many centers either are cautious with or exclude patients over the age of 70 years. A few studies examining clinical outcomes in patients over the age of 70 years have reported similar improvement in motor scores and dyskinesia [25, 27, 28]. However, quality of life did not improve significantly [25, 28]. Duration of PD symptoms by itself is inadequate to guide patient selection. With short duration of disease, there is a risk of implanting patients with atypical parkinsonism, whereas patients with disease duration of 15 to 20 years may have symptoms which respond poorly to DBS. After the results of the EARLYSTIM trial, the therapeutic window of DBS has been expanded to include patients with motor fluctuations with at least 4 years of disease duration [29].

For optimizing patient selection, a multidisciplinary team approach is recommended followed by a detailed multidisciplinary review to reach a final consensus plan about target selection, unilateral *versus* bilateral procedure, and type of DBS system.

Target Selection

The two targets most frequently used for DBS electrode implantation in PD are the globus pallidus interna (GPi) and the subthalamic nucleus (STN). Both targets have been evaluated in several studies and demonstrated comparable improvement in motor symptoms and quality of life [30–34]. Recently, a meta-analysis found similar efficacy of STN and GPi in long-term tremor suppression [35]. Both targets significantly reduce levodopa-induced dyskinesia; however, GPi stimulation can have a greater anti-dyskinetic effect [30, 32–34]. An anti-dyskinetic effect is related to direct stimulation of pallidofugal fibers with GPi-DBS and medication reduction after STN-DBS (although stimulation dorsal to the STN can also activate pallidothalamic fibers) [36]. Across multiple studies, STN-DBS has consistently been associated with greater reduction in dopaminergic medications compared to GPi-DBS [30, 33, 34, 37]. Reduction in medication dose can reduce dyskinesia and other medication-induced side effects including drowsiness, compulsive behaviors, orthostatic hypotension, and hallucinations.

DBS effects on gait and axial symptoms assessed by Unified Parkinson Disease Rating Scale (UPDRS) II and III subscores showed no difference between the two targets [33, 38]. However, GPi-DBS together with levodopa was reported to maintain improvement in gait and posture up to 5 years, whereas a decline after 2 years was noted with STN-DBS [39]. The reason for the differential effect on gait is not clear and could potentially be related to higher dopaminergic medications with GPi-DBS or a direct neuromodulatory effect of different targets on gait neural networks. These findings suggest that GPi-DBS may be a superior target for PD patients with postural instability and gait difficulty, although with both targets improvement in gait and posture declined in the long term [39].

There is limited literature on the effects of different targets on cognition and neuropsychiatric symptoms. The VA cooperative study assessed cognitive measures and found a significant worsening in the Mattis Dementia Rating Scale (MDRS) and Hopkins Verbal Learning Test with STN-DBS as compared to GPi-DBS at 36 months [32]. However, as the STN-

DBS group had worse baseline cognitive measures, these results should be interpreted carefully [32]. In the COMPARE trial, the effect of unilateral GPi *versus* STN showed no difference on primary mood and cognitive outcomes, though its secondary outcome analysis showed worse cognitive issues after STN-DBS [31]. Recently, the NSTAPS study reported no significant difference in global cognitive function, psychiatric symptoms, and neuropsychological assessments between the two targets (STN *vs* GPi) at 3 years [40]. In a meta-analysis of several randomized clinical trials, STN-DBS was associated with a decline in phonemic fluency, attention, working memory, and processing speed; however, no difference in quality of life and psychiatric symptoms was seen between the two targets [41].

Other DBS targets are less often utilized or are under investigation presently. The ventral intermediate nucleus of the thalamus (ViM) is an established target for tremor control, but it is considered less frequently as it has a limited effect on other motor symptoms and does not improve motor complications. ViM-DBS is used in some patients with tremor-dominant PD [42, 43]. Several small studies that investigated the pedunculopontine nucleus (PPN) as a potential target for freezing of gait (FOG) and postural instability in PD have reported variable outcomes [44–47]. The posterior subthalamic area (PSA)/cZi (caudal zona incerta) has been reported to be an effective target for parkinsonian tremor [48–50]. The thalamic centromedian-parafascicular complex (CM/Pf) has also been suggested as a potential target because of its anatomical connections to different cortical and subcortical motor areas [51, 52].

Unilateral *Versus* Bilateral Surgery

Determination about unilateral or bilateral lead placement is done during preoperative evaluations. Most centers perform bilateral lead placement as a majority of patients have axial and bilateral symptoms. Lead implantation can be performed simultaneously during a single session or in a staged approach with placement of a lead for the most affected side first followed by the contralateral side after several weeks or months. The literature on staged compared to simultaneous approach for lead placement is limited. A staged procedure may potentially reduce the risk of DBS-associated complications and recovery time [53]. However, a retrospective analysis comparing staged and simultaneous approach found no significant difference between 90-day postoperative complications and annualized cost [54]. For older patients or those with predominant one-sided symptoms, unilateral DBS may be considered [55, 56]. Unilateral DBS in either STN or GPi has been shown to improve motor symptoms and quality of life [56, 57], with a greater benefit with GPi-DBS on quality of life [58].

Hardware Selection

The principal components of DBS hardware include intracranial electrode leads, an implantable pulse generator (IPG), and extension wires connecting intracranial leads to the IPG. With innovation in DBS technology, there has been an advancement in both electrode design and IPGs. DBS leads have evolved from vertically aligned conventional quadripolar (4-contact) ring-shaped electrodes to leads with octopolar (8-contact) and segmented electrodes (directional leads). The directional leads consist of 2 middle contacts with 3 radially segmented electrodes at 120° and 2 ring-shaped electrodes at the highest and lowest contacts (1-3-3-1) [59]. With stimulation of individual or a combination of segmented electrodes, the current can be steered in a particular direction–"directional stimulation." Newer devices allow constant current stimulation and multiple independent current control (MICC) in which each electrode has a dedicated current source [60]. These advancements have enhanced programming capabilities by enabling complex field shaping to avoid stimulation-induced adverse effects and optimize clinical benefits [61–63] but have also increased the amount of time clinicians require for programming [64].

Presently, 3 FDA-approved DBS systems are commercially available in the USA (Table 1). All DBS devices have similar efficacy, and selection of the DBS system is based on individual patient factors and experience of the DBS center with different devices. Although current steering and MICC capabilities offer an advantage over conventional DBS systems to reduce stimulation-induced adverse effects, its long-term utility in clinics is yet to be determined. Other factors such as MRI compatibility and patient preference for rechargeable IPGs could be considered in the selection process.

Surgical Procedure

Different surgical techniques are utilized to implant DBS leads. The choice of technique differs across centers and is determined by the surgical team based on their training and experience [65]. During the surgical procedure, the DBS target is defined either by predefined stereotactic atlas-based coordinates (indirect targeting) or by direct visualization on imaging (direct targeting). Various stereotactic frames are commercially available to assist in accurate lead placement in the selected target [65]. Frameless stereotaxy which was introduced recently has similar lead placement accuracy and obviates patient discomfort caused by the stereotactic frame [65]. Traditionally, most centers perform awake surgeries with intraoperative physiological mapping, including microelectrode recording (MER) and/or macrostimulation to refine the anatomical target, during which patients participate in neurological assessments [66]. Recently, with improvement in imaging, some centers perform lead placement with direct targeting

Table 1 Currently available DBS devices in the USA

	Medtronic, Minneapolis, MN, USA	Abbott Medical, Plano, TX, USA	Boston Scientific, Valencia, CA, USA
FDA-approved target	STN, GPi, Vim	STN, GPi	STN
Lead design	4-ring electrode (1-1-1-1)	Directional (1-3-3-1)	8-ring electrodes and directional (1-3-3-1)
IPGs			
Current source	Single	Single	MICC
Nonrechargeable	Activa SC and PC	Infinity	Vercise PC
Rechargeable	Activa RC	NA	Vercise, Vercise Gevia
Programming			
Amplitude (mA or V)	Constant voltage or current	Constant current	Constant current
Frequency (Hz)	2-250	2-240	2-255
Pulse width (μs)	60-450	20-500	20-450
MRI compatibility	Full body (newer models)	Full body	Full body (only Gevia)

during asleep procedures using intraoperative imaging such as intraoperative O-arm, intraoperative CT (iCT), or intraoperative MRI (iMRI) to confirm lead placement [67–69]. These surgeries can be performed under general anesthesia without intraoperative physiological mapping and/or test stimulation.

Preference regarding MER-guided awake *versus* asleep procedure without MER guidance for lead placement is a matter of ongoing debate [70]. Neurophysiological mapping such as MER and/or macrostimulation during an awake procedure can assist in verifying the selected target and optimizing lead placement [66]. In one study, 20% of the initial trajectories for the DBS target based on imaging alone were identified to be suboptimal and were revised subsequently using MER guidance [71]. Results of intraoperative test stimulation can aid in determining optimal stimulation parameters during programming [72]. However, MER has been associated with an increased risk of hemorrhage [73] and can increase the duration and cost of surgery [70]. Also, awake surgeries can be inconvenient for patients with severe procedure-related anxiety and major discomfort in the off-medication state. Both MER-guided awake procedure and imaging-guided asleep procedure (iMRI or iCT) have shown comparable clinical outcomes and lead accuracy [74, 75]. A meta-analysis comparing awake and different asleep procedures showed no significant difference in clinical outcomes, lead accuracy, and surgery duration. The study found an increased risk of complications including infection and hemorrhage with the awake procedure and an increased risk of stimulation-induced side effects with the asleep procedure [76]. However, only 16/145 studies utilized asleep procedures, and imaging protocols varied widely [76].

There is no clear consensus on the best technique for lead placement. The surgical technique should be chosen based on the surgeon's experience and comfort level, and by considering patient-related factors. For example, at centers with availability of different techniques, asleep surgeries could be considered in patients who do not prefer or tolerate the awake procedure, whereas preference for an MER-guided awake procedure can be potentially given for patients who could not tolerate general anesthesia. Further studies across multiple centers assessing different techniques and patient-related factors may help in guiding DBS teams in selecting the most appropriate procedure.

DBS Programming and Medication Management

After successful placement of the DBS system, the efficacy is dependent on programming along with careful medication adjustment. DBS programming is performed by trained clinicians (neurologists, nurses, physician assistants, etc.) who understand DBS systems, target anatomy, stimulation-induced side effects, and medication adjustment. Initial programming is typically performed 2 to 4 weeks after lead placement, allowing time for resolution of microlesion benefit. Input from intraoperative test stimulation and/or postoperative imaging with DBS leads overlaid on deformable atlases can assist in DBS programming and increase efficiency [72, 77].

Initial monopolar review is performed by systematically screening each individual electrode for potential benefits and side effects to determine the therapeutic window (amplitude threshold for side effects minus benefit threshold). This is performed in monopolar mode by assigning one of the electrodes with negative polarity (cathode) and the neurostimulator with positive polarity (anode). Amplitude is slowly increased while keeping other parameters (frequency, pulse width) constant to determine the therapeutic window for each electrode. In case of stimulation-induced side effects, available strategies include adjusting different stimulation parameters (amplitude, pulse width, frequency), switching to a different electrode, or bipolar mode. Advanced programming such as interleaving, current steering, and adjusting the proportion of the current on different electrodes with MICC stimulation can be explored to optimize

outcomes. Stimulation is adjusted during follow-up visits based on clinical response and progression of symptoms.

Dopaminergic medication can be potentially reduced after DBS surgery. The reduction in dopaminergic medications is greater with STN-DBS as compared to GPi-DBS [30, 33, 34, 37]. Medication reduction is performed gradually, and patients are monitored for worsening of any non-motor issues (e.g., depression, sleep difficulty, restless legs, etc.). Although, in patients experiencing severe STN-DBS-induced dyskinesia, relative rapid reduction of medications can be performed carefully.

Clinical Outcomes

Multiple studies have consistently demonstrated the efficacy of DBS in PD [26, 78–81] using UPDRS scores, motor diaries, PD quality of life questionnaire (PDQ-39), and various neuropsychiatric scales. As summarized in Table 2, evidence from multiple randomized clinical trials with both STN-DBS and GPi-DBS has shown improvement in motor scores, increased "on time" without troublesome dyskinesia, and quality of life (QOL). Deuschl and colleagues [78] conducted the first multicenter randomized controlled clinical trial and reported significant improvement in off medication UPDRS part III motor scores (41%) with STN-DBS as compared to best medical therapy (BMT). Also, there was significant improvement in QOL (24%) in patients with STN-DBS as compared to no change in patients who were on BMT [78]. In the VA Cooperative Study, at 6-month follow-up, STN-DBS showed an increase in "on time" without troublesome dyskinesia by 4.6 h and QOL improved significantly (17%) as compared to no change with BMT [26]. PD SURG trial found greater improvement in QOL with medical therapy combined with DBS as compared to medical therapy alone (13.3% *vs* 1.5%) [82]. Although, in most of the early studies, STN was the preferred DBS target, subsequent studies showed similar improvement with GPi-DBS [33, 37]. The effect of DBS therapy on motor outcomes can be sustained over 10 years; however, the improvement in quality of life wanes over that time [83, 84].

Complications

In appropriately selected patients, DBS surgery is well tolerated and relatively safe; however, complications associated with surgical procedure and implanted hardware may occur. Complications include intracranial hemorrhage (1-5%), stroke (0-2%), infection (2-5%), seizure (0.3-5%), perilead edema (3-4%), postoperative confusion (5-26.5%), and rarely death [85–90]. Novel complications such as delayed intracerebral cystic lesions have also been described [91]. Recently, loss of swimming skills after STN-DBS was reported in 9 patients [92]. Of the hardware-related complications, infection and pain at the neurostimulator site are most common. Other hardware-related complications include lead fracture, erosion, lead migration, and lead misplacement [85–88, 90]. Lead misplacement occurs in 1.7 to 2.2% of leads [85–87] and is one of the common reasons for poor outcomes [20]. In a study analyzing two large national databases, the rate of revision and removal was reported in 15.2 to 34% of implanted leads and 48.5% of revisions were due to improper target and lack of therapeutic effect [93].

Stimulation-related side effects vary based on the DBS target because of the spread of the electrical current into the surrounding regions/tracts. These can be divided into sensory or motor and neuropsychiatric side effects. As mentioned in previous sections, STN-DBS is associated with impairment in verbal fluency and other select neurocognitive measures [39, 41]. It is advised to monitor neuropsychiatric symptoms such as depression, anxiety, and behavioral changes carefully during adjustment of DBS parameters and dopaminergic medications. Suicide rates with STN-DBS have been reported to be < 0.5% [94], although results from randomized controlled trials did not support a direct association between suicide risk and DBS surgeries [95].

Mechanisms of Action

Contemporary clinical DBS developed out of a largely serendipitous observation that high-frequency (> 100 Hz) stimulation alleviates tremor [6]. The last three decades of research have led to increased understanding of DBS mechanisms locally in the immediate vicinity of the stimulating electrode and network-wide [96]. Clinical effects of DBS and lesioning are similar, which led to the initial hypothesis that DBS inhibited local neurons [97, 98]. However, activity is increased in the downstream nuclei during stimulation [99]. The apparent paradox of simultaneous cell body inhibition and axonal activation was explained in part by computational modeling studies demonstrating that under extracellular electrical stimulation, the action potential initiates in the axon [100]. Although basal ganglia activity is pathologically increased in PD, it was proposed that by regularizing basal ganglia output by DBS, an "informational lesion" is created allowing normalized sensorimotor processing through the motor network [101].

Additionally, PD has been characterized by exaggerated oscillatory neural activity in the beta (13-30 Hz) band within and between the motor network nuclei. Both levodopa and DBS reduce this excessive synchronized activity leading to improved motor function [102, 103]. It is still unclear how an increase in local neural activity surrounding the DBS electrode leads to this beneficial desynchronization. Furthermore, different PD symptoms respond to DBS at different time courses. This suggests that not only does stimulation serve as an on–off switch for modulating circuit oscillations, but that it may also induce synaptic reorganization and alter gene expression [104].

Table 2 Summary of DBS randomized clinical trials

Study	Comparison	No. of subjects	Mean age (years)	Duration (months)	Outcomes
†Deuschl et al., 2006 [78]	DBS (STN) *versus* BMT	78 *versus* 78	60.5	6	*PDQ-39 SI: 24% *versus* NC *UPDRS III off meds: 41% *versus* 1.7%
†Witt et al., 2008 [80]	DBS (STN) *versus* BMT	60 *versus* 63		6	*MDRS: NC Verbal fluency: worse in DBS Stroop test: worse in DBS
Schupbach et al., 2007 [79]	DBS (STN) *versus* BMT	10 *versus* 10	48.4	18	*PDQ-39 SI: 24% *versus* NC UPDRS III off meds: 69% *versus* − 29%
Weaver et al., 2009 [26] VA Cooperative Study	DBS (STN or GPi) *versus* BMT	121 *versus* 134	62.4	6	*Improvement in "on time" without troublesome dyskinesia: 4.6 *versus* 0 h UPDRS III off meds: 28.6% *versus* 4% PDQ-39 SI: 17.1 *versus* NC
Williams et al., 2010 [82] PD SURG trial	DBS (STN or GPi) + BMT *versus* BMT	178 *versus* 171	59	12	*PDQ-39 SI: 13.3% *versus* 1.5% UPDRS III off meds: 35.7% *versus* 2.6% MDRS: no change
Okun et al., 2012 [81]	DBS (STN) *versus* delayed DBS Off/On	101 *versus* 35	60.6	3–12	*Improvement in "on time" without troublesome dyskinesia at 3 months: 4.27 *versus* 1.7 h UPDRS III off meds: 39.2% *versus* 8%
Schuepbach et al., 2013 [29] EARLYSTIM Study	DBS (STN) *versus* BMT	124 *versus* 127	52.9	24	*PDQ-39 SI: 26% *versus* NC% UPDRS III off meds: 52.7%. *versus* 3.6%
Randomized clinical trials comparing different targets					
Anderson et al., 2005 [30]	STN *versus* GPi	12 *versus* 11	STN, 61 GPi, 54	12	*UPDRS III off meds: 48% *versus* 39% ($p = 0.40$) LEDD reduction: 38% *versus* 3% ($p = 0.08$)
†Follett et al., 2010 [37]	STN *versus* GPi	147 *versus* 152	STN, 61.9 GPi, 61.8	24	*UPDRS III off meds: 28.2% *versus* 25.3% ($p = 0.5$) PDQ-39 SI: NC MDRS global: NC Processing speed index: STN worse
†Weaver et al., 2012 [32]	STN *versus* GPi	70 *versus* 89	STN, 60.7 GPi, 60.4	36	*UPDRS III off meds: 30.1% *versus* 34.1% ($p = 0.59$) PDQ-39 SI: NC MDRS: worse for STN
Okun et al., 2009 [31] COMPARE trial	Uni STN *versus* Uni GPi	22 *versus* 23	STN, 59.8 GPi, 60.2	7	*VAMS: NC *Verbal fluency: letter verbal fluency worse for STN ($p = 0.03$) UPDRS III off meds: 29.9% *versus* 26.6% ($p = 0.64$)
Odekerken et al., 2016 [33] NSTAPS study	STN *versus* GPi	43 *versus* 47	STN, 60.9 GPi, 59.1	36	*UPDRS III off meds: 31.7% *versus* 23.2% ($p = 0.04$) *Composite score (mood, cognitive, behavioral effects): NC ($p = 0.69$)

NC = no change, BMT = best medical therapy, STN = subthalamic nucleus, GPi = globus pallidus pars interna, PDQ-39 SI = Parkinson disease questionnaire summary index, MDRS = Mattis Dementia Rating Scale, VAMS = visual analog mood scale

*Primary outcome

† Same patient cohort and study group

Future Directions

Currently available clinical DBS devices deliver a continuous train of electrical pulses at preset amplitude, pulse width, and frequency. However, the severity of PD symptoms varies over the course of the day because of physiologic fluctuations and medication intake. As a result, there has been a great interest in developing adaptive (closed-loop) DBS devices that can automatically change stimulation settings based on the patient's clinical status. This requires an objective marker of disease or symptom severity that can be continuously monitored. Pilot studies have been performed using beta band oscillations as a marker of akinesia rigidity [105], gamma band oscillations as a marker of dyskinesia [106], and externally recorded accelerometer signal as a marker of tremor severity [107]. Technical challenges and incomplete understanding of potential biomarkers have hampered adoption into clinical practice.

The ideal PD therapy would slow down or even reverse disease progression. Animal studies have suggested that electrical stimulation may have such effect [108, 109]. This led to a pilot study in patients with very early PD in hopes that DBS would provide disease-modifying benefit rather than just symptomatic treatment as it is used today. This study was primarily focused on safety and feasibility, but it showed potential slowing of rest tremor progression in patients with STN-DBS compared to medication therapy alone in a *post hoc* analysis. However, there was no significant difference in UPDRS motor scores and quality of life between the 2 groups. Also, the study has limitations including small sample size and open-label design; therefore, currently, there is insufficient evidence to support neuroprotective effect, and a larger clinical trial is planned [110].

Lesioning Procedures

Lesioning or ablative surgeries (LS) involve selective destruction of a targeted brain tissue volume in order to interrupt maladaptive neural networks. Although LS have been performed for several decades in selected patients with PD, their use decreased in the 1960s after the introduction of levodopa and then again in the 1990s because of DBS. The field of LS has since grown, and currently available techniques include radiofrequency (RF) thermoablation, stereotactic radiosurgery (SRS), MRI-guided high-intensity focused ultrasound (HIFU) thermal ablation (or MR-guided focused ultrasound, MRgFUS), and laser interstitial thermal therapy (LITT), with the former three being used commonly in movement disorders (Fig. 1) [111]. SRS and HIFU are considered less invasive than radiofrequency lesioning because they do not require a burr hole or an intracranial probe.

Patient Selection

Despite the fact that most clinicians favor DBS over LS wherever the former is widely available, LS is still utilized in less developed countries because of lack of appropriate infrastructure and training, financial constraints, limited research, awareness and referrals to tertiary centers, and follow-up care for DBS [112].With advancement in imaging and localization approaches, LS remains an alternative therapeutic option for PD management. LS can be considered in patients who choose not to or cannot safely undergo DBS surgery and/or have difficulties with regular follow-up programming visits [113]. Criteria for LS candidacy are similar to those of DBS, and a multidisciplinary evaluation by a movement disorders neurologist, a neuropsychologist, and a neurosurgeon to determine the appropriateness of the therapy and target selection is recommended. Compared to DBS, successful LS is relatively cheaper and reduces postoperative care and hardware-related complications [114]; however, LS is not reversible and postprocedure optimization is not possible without revision surgery. A major limitation of LS is increased side effects with bilateral lesions, including aphasia, dysarthria, dysphagia, and cognitive deficits about 30 to 60% for bilateral thalamotomies and hypophonia, neuropsychological, and cognitive deficits about 17% for bilateral pallidotomies [115–121]. Unilateral lesioning can be followed by contralateral DBS in patients who are appropriate candidates [122, 123].

Target Selection

Studies involving RF ablation, SRS, and HIFU have proven benefit with thalamotomy for tremor-dominant PD and pallidotomy for medication-resistant motor fluctuations. Due to concern of intractable hemiballismus with subthalamotomies, STN has been less studied for LS in PD, although recent studies have demonstrated significant improvement in motor symptoms with minimal development of hemiballismus [124–127]. Generally, thalamotomy is considered for tremor-predominant PD or ET, although in patients with PD, a pallidotomy might be a better choice as it can additionally improve bradykinesia and rigidity. As the data for LS utilizing STN as the target is limited, presently it is considered infrequently.

Radiofrequency Lesioning

Similar to DBS, this surgical method includes neuroimaging, a stereotactic headframe, and introduction of an electrode intracranially coupled to an RF generator. Patients are awake during the procedure and a test stimulation is done to confirm the target. A thermally induced lesion is then achieved at the

tip of the active electrode with alternating current. The electrode is retracted after lesioning is complete. RF lesioning allows distinct lesion borders with immediate results, thus allowing intraoperative confirmation of symptom improvement. ViM thalamotomy for tremor-predominant PD has shown immediate tremor improvement ranging from 60 to 100% using RF ablation [128, 129], including long-term benefit of 57 to 90% for 2 to 15 years [129–131]. Most side effects for thalamotomy, including ataxia, dysarthria, and sensory/motor deficits, are related to perilesional edema which subsides over time, usually over 1 week to 1 month, but are variable depending on the lesion size [132]. Studies involving unilateral pallidotomies with RF for PD have shown an average reduction of 30% in UPDRS III motor scores with improvement for tremor, bradykinesia, rigidity, gait, and balance [117, 133–135]. There is also improvement in dyskinesia up to 90% [136, 137]. Adverse effects of pallidotomy include visual field deficits, paresis, and neuropsychological deficits, and they are mostly transient due to perilesional edema of variable duration [116, 138–140]. The surgical risk associated with RF technique also includes hemorrhage and infection [141].

Stereotactic Radiosurgery Lesioning

SRS lesioning involves a single large dose of ionizing radiation delivered noninvasively to a limited intracranial target volume using computerized dosimetry planning and image-guided stereotaxy. Different devices are used to deliver radiation, including GammaKnife ® and linear accelerators. Drawbacks associated with SRS include lack of intraoperative feedback, variable lesion size, poorly defined lesion borders, exposure to ionizing radiation, and delayed effect [111]. The median onset of benefit is around 2 months and benefits are sustained long term (median 30 months) [142, 143]. A study has reported complete or near complete improvements in tremor in about 88% patients with PD with SRS thalamotomy [143]. SRS has also been shown to have a similar efficacy and safety profile to RF lesioning and DBS therapies for pallidal lesions [143, 144].

Focused Ultrasound Thermal Ablation

FUS utilizes high-intensity focused ultrasound beams targeted to an intracranial region to perform thermal ablation. With the use of MRI-guidance and MR-thermography, accurate targeting and real-time monitoring of the lesion are possible, and this approach, called MR-guided FUS (MRgFUS), has reignited interest in lesioning procedures for movement disorders [111]. An array of transducers in a helmet is used to pass ultrasonic waves through the skull into a target in the brain. Advantages of this technique include lack of ionizing radiation, immediate results, ability to produce well-circumscribed lesions, and real-time MRI monitoring. Limitations include MRI environment–related claustrophobia in patients and longer operative times [111, 145]. Another limitation of MgFUS is that the ability to produce effective lesions depends on skull thickness/density. Currently, MRgFUS is FDA approved for unilateral thalamotomies in ET and tremor-predominant PD. Its use in pallidotomies and subthalamotomies is under investigation. In several studies, MRgFUS thalamotomies for tremor-predominant PD have shown improvement from 30 to 60% in UPDRS III motor score [146–148]. Similar results have been reported with MRgFUS pallidotomies [149, 150]. In a recent unblinded open-label study with MRgFUS subthalamotomy, 9 patients who underwent modified protocol MRgFUS showed an improvement of 60.9% in UPDRS III motor scores at 3 months [151]. Another study targeting the STN with MRgFUS in 10 patients reported 53% improvement in UPDRS III motor scores at 6 months without significant side effects [127]. In this study, there were a total of 38 adverse events over a 6-month follow-up period. Of these, there were three events which were related to the STN lesioning directly: off-medication choreic dyskinesia, on-medication nondisabling dyskinesia, and subjective speech disturbance. The two patients with dyskinesia had near resolution of symptoms at 6 months after the medications were adjusted [127].

How to Choose Among Surgical Therapies in PD

Different surgical treatment options can be considered in selected PD patients to improve motor symptoms that are poorly controlled with oral medications. Both DBS or lesioning surgeries have shown to reduce "off time" and dyskinesia, treat medication-resistant tremor, and improve quality of life. Deciding on a specific therapy requires a multidisciplinary team and is tailored towards the individual patient, based on their symptoms, expectations, risk–benefit ratio, and local expertise.

In healthcare systems where DBS is readily available, it is generally preferred over lesioning procedures because stimulation effects are adjustable and DBS can be safely performed bilaterally. Lesioning procedures may be appropriate for patients who may not tolerate DBS hardware (e.g., history of head and neck cancer or repeated DBS hardware infections), have surgical contraindication (e.g., a blood vessel in the trajectory of the targeted area), are unable to attend frequent clinic visits for programming, or are unwilling to deal with hardware maintenance and potential complications. A well-placed lesion can provide excellent motor benefit, but it is less

forgiving if suboptimal. Bilateral lesions should not be performed because of a high risk of complications, especially for pallidal and thalamic targets. The exact type of lesioning procedure offered will usually depend on local expertise. Many centers performing awake, MER-guided DBS implantations will offer RF ablations. MRgFUS is increasingly attractive to patients because it does not require an incision, although access is still limited because of high equipment costs. Radiotherapy is typically less favored given the less predictable lesion size and delayed onset of benefit, but it may be a good option for patients who are unable to undergo DBS or other lesioning procedures.

Utilizing DBS in a patient who had a prior lesioning procedure can provide additional therapeutic benefit, and it may be considered in select cases. This assumes that the patient is able to undergo DBS procedure even though lesioning was preferred as the initial treatment. For example, a patient may have initially chosen to undergo lesioning to avoid frequent clinic visits for programming and hardware maintenance, but eventually developed troublesome contralateral symptoms, or had unilateral surgical contraindication for DBS. Utilizing DBS is expected to reduce the chance of adverse events such as speech and cognitive difficulties observed after bilateral lesioning surgeries. Additionally, DBS can be considered as a rescue therapy for patients who had previously undergone lesioning and had suboptimal benefit, recurrence of symptoms, or certain side effects. For example, a lesion-induced dyskinesia from a subthalamotomy could be improved by pallidal DBS. Conversely, if there have been repeated infections with DBS hardware, a patient may benefit from lesioning procedure (even utilizing the existing DBS lead to create a lesion).

Patients with significant cognitive impairment, those with unstable psychiatric symptoms (including hallucinations), or those with significant medical comorbidities are not good surgical candidates for DBS or lesioning procedures. Some patients may opt against neurosurgical procedures based on personal beliefs and risk tolerance. For those patients, other advanced therapies including levodopa–carbidopa intestinal gel infusion (LCIG) or continuous subcutaneous apomorphine infusion (CSAi) options should be considered. An in-depth discussion of infusion devices is beyond the scope of this review article, but a brief comparison of surgical procedures with other advanced therapies is presented in Table 3.

Specific motor symptoms may respond to a different degree following DBS or lesioning procedure. Tremor, dyskinesias, and rigidity respond very well, followed by bradykinesia, then gait and other axial symptoms. Gait difficulty and freezing of gait will typically respond if they are levodopa responsive, but many patients either have or eventually develop nonresponsive features, whereas balance typically does not improve. Given the unsatisfactory response of gait and balance to current treatments, more research is needed for experimental therapies such as motor cortex and spinal cord stimulation. Finally, as none of the therapies have clearly shown to be neuroprotective, further research is needed to understand their role in altering the disease course and the development of disease-modifying therapies.

In conclusion, there is a wide range of surgical therapy options for management of PD. Applying these techniques requires a skilled multidisciplinary team to help a patient choose the appropriate therapy, perform the intervention, and offer a long-term comprehensive follow-up.

Table 3 Comparison of surgical therapies with other advanced treatments for PD

Treatment	Indications	Advantages	Limitations
DBS	Motor fluctuations and dyskinesia Medication-refractory tremor	Superior to BMT Adjustable and reversible Superior for medication-refractory tremor	Invasive therapy Poor axial symptom control Not indicated for patients with dementia
Lesioning surgeries	Motor fluctuations and dyskinesia Medication-refractory tremor	Less postoperative care No hardware-related complications Less frequent follow-ups	Irreversible lesion Not modifiable as the disease progresses Not recommended bilaterally
LCIG	Motor fluctuations and dyskinesia Poor DBS candidates or who do not prefer DBS	Simulates physiological dopamine release Less invasive than DBS May provide better axial symptom control No age limits Can be considered in mild to moderate dementia and depression	Dopaminergic-related side effects Increase patient or caregiver burden
*CSAi	Motor fluctuations Off episodes Poor DBS candidates or who do not prefer DBS	Mildly invasive parenteral administration Avoid GI-related absorption issues Can be considered in mild dementia and depression	Tolerability issues May need frequent blood tests Increase patient or caregiver burden

DBS = deep brain stimulation, LCIG = levodopa–carbidopa intestinal gel, CSAi = continuous subcutaneous apomorphine infusion

*Currently not FDA approved

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