Surgical Treatment of Levodopa-induced Dyskinesia in Parkinson's Disease

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Abstract

The treatment of motor manifestations of Parkinson's disease (PD) is essentially a trade-off between adequate relief of motor symptoms and prevention and control of motor complications, particularly levodopa-induced dyskinesia (LID). Progression of PD is paralleled by a progressive difficulty in achieving the balance. Functional neurosurgical procedures provide sustained relief of LID in carefully selected patients when further tailoring of medical therapy fails to achieve this goal. Though deep brain stimulation (DBS) has superseded lesioning surgeries, pallidotomy still has a role in those patients in whom DBS is not feasible for financial or other reasons.

Keywords: Deep brain stimulation, levodopa-induced dyskinesia, pallidotomy, Parkinson's disease

Introduction

Parkinson's disease (PD) is no longer considered a pure movement disorder. It is now recognized as a multisystem neurodegenerative disease with a long premotor phase and protean nonmotor manifestations. However, motor dysfunction is pivotal in the early and mid-stages of the disease and a major contributor to disability. A successful neuroprotective therapy continues to be an unmet need in the management of PD. Despite this, PD differs from most other neurodegenerative diseases in that highly effective pharmacotherapy is available to control the cardinal motor symptoms. This somewhat unique feature of PD is attributable to its motor dysfunction linking strongly with nigrostriatal dopaminergic denervation.[1,2] The relatively preserved postsynaptic mechanisms allow exogenous dopaminergic agents to compensate effectively for the presynaptic dopaminergic terminal loss, at least during the initial stages of the disease. In accordance with this, levodopa continues to be the backbone of pharmacotherapy of this condition ever since its introduction for clinical use in PD, more than four decades ago.[3,4]

The "honeymoon" period characterized by improved quality of life (QOL) facilitated by stable reduction of motor symptoms with dopaminergic therapy wanes off after the initial few years.[5] Motor complications ("wearing off" and more complex and unpredictable motor fluctuations and levodopa-induced dyskinesia – [LID]) emerge as a clinical problem in around half of the patients after 5 years of dopaminergic therapy and in almost all, after a decade.[6] These become progressively difficult to treat pharmacologically. This review focuses on the surgical options to manage LID.

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Challenges in the Pharmacological Management of Levodopa-induced Dyskinesia

Nearly 90% of patients treated with levodopa develop LID after 10 years of therapy.[7] The pathophysiological mechanisms underlying LID are largely irreversible once they are established. The pharmacological strategies aimed at delaying the emergence of LID and their suppression once they have emerged, discussed in detail in another review in this series, have their own inherent limitations. The limitations stem from the inexorable progression of the neurodegeneration underlying PD contributing both to progressive worsening of parkinsonian symptoms as well as LID, and the fact that successful control of dyskinesia by manipulation of

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dopaminergic treatment is possible on the majority of occasions only at the cost of a poorer control of parkinsonian symptoms. The anti-parkinsonian effects of dopaminergic treatment are coupled with dyskinesia,[8] and clinical trials of various pharmacological interventions in PD have shown parallel increase in dyskinesia with increase in "on" time.[9] Delaying the initiation of levodopa and prolonging "levodopa-sparing therapy" aiming at prevention of emergence of motor complications are unacceptable to most patients as well as to movement disorder neurologists treating patients with PD. The parkinsonian symptoms, rather than LID, affect functioning and QOL more, particularly in earlier stages of PD.[10] Patients initiated on levodopa early have accordingly been shown to have better QOL compared to levodopa-sparing therapies, and the adverse effects of these therapies and cost are additional concerns.[11,12] Moreover, most (if not all) patients with PD will ultimately require levodopa; LIDs emerge faster in more advanced stages of PD when levodopa is initiated because of unavoidability, irrespective of a prolonged levodopa-sparing therapy initially at the cost of reduced QOL.[13] Occurrence of clinically significant and disabling LID is unaffected by delaying levodopa treatment as severity of neurodegeneration plays a more important role in this type of LID.[14-16]

Thus, pharmacological interventions targeting the dopaminergic mechanisms underlying LID are unlikely to remain successful for prolonged periods, as the control of LID achieved by this strategy is at the cost of poorer control of parkinsonian symptoms. Therapies addressing the nondopaminergic mechanisms, with the exception of amantadine, are yet to show promising and clinically relevant results. Functional neurosurgery, particularly deep brain stimulation (DBS), is currently the standard of care for patients with moderately advanced stages of PD in whom LID has a dose-limiting effect on dopaminergic treatment.

Surgical Treatment of Levodopa-induced Dyskinesia

Ablative surgeries for control of parkinsonian symptoms were encouraged by serendipitous observation of relief of tremor by ligation of the anterior choroidal artery to control bleeding.[17] The interest subsequently shifted from ablation of the globus pallidus internus (GPi) (pallidotomy) to thalamotomy, as tremor control was thought to be better with the latter. The spurt of interest in ablative procedures for PD which occurred in the 1950s dwindled away following the introduction of levodopa and the robust symptomatic improvement provided by it, only to re-emerge later in the early 1990s as a treatment of motor complications of levodopa.[18,19] The concept of DBS also evolved from serendipity – suppression of tremor by high-frequency stimulation was noted during intraoperative stimulation for clinical localization prior to thalamotomy.[20] The current era of neurostimulation for movement disorders was ushered in by Benabid's report of the efficacy of chronic thalamic stimulation to control tremor in PD.[21] With the rapidly increasing popularity of DBS, ablative surgeries limited by concerns on irreversibility and adverse effects when done bilaterally are again facing a diminished interest; however, they still have a role in selected patients where DBS is contraindicated or financially not feasible, particularly in resource-poor countries.

Deep Brain Stimulation

The DBS hardware essentially consists of highly specialized electrodes (leads) with the active tips implanted in the target and the extracranial ends connected to an implanted pulse generator ([IPG] or "Neurostimulator") using extension cables [Figure 1]. The stereotactic implantation of DBS leads is guided by microelectrode recording from the target and intraoperative macrostimulation for assessing improvement of parkinsonian signs and presence of any adverse effects related to stimulation. The pulse generator, conventionally implanted in a left infraclavicular pocket by most centers doing the procedure, can be precisely programmed to deliver electrical stimulation of the target areas continuously so as to have optimal symptom control and no/minimum adverse effects due to spread of stimulation to neighboring neural structures. The advantages of DBS compared to lesioning surgeries discussed later are (1) reversibility, as no significant permanent damage is produced in the target in an uncomplicated surgery done by experienced centers, (2) can be done bilaterally for control of bilateral and axial symptoms, and (3) adverse effects resulting from stimulation and new or worsening parkinsonian symptoms arising from disease progression could be managed by programming the pulse generator and modifying the parameters of neurostimulation.[18]

DBS is currently regarded as the standard of care for patients with mid-stages of PD experiencing motor complications of levodopa treatment. All patients with PD are not DBS candidates; patient selection is one among the most important factors which determine the success of this stereotactic neurosurgical procedure aimed at controlling the motor symptoms. The factors to be considered in patient selection are shown in Table 1. It is a relatively safe procedure in experienced hands, with severe adverse effects occurring

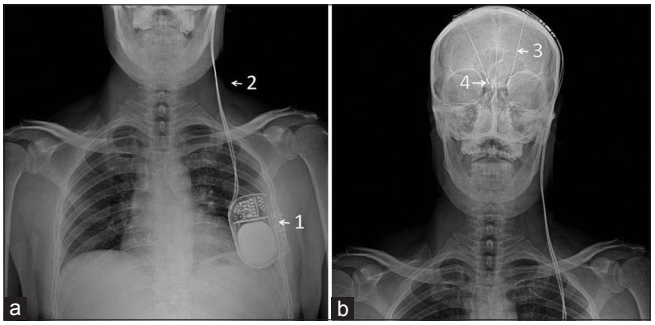

Figure 1: X-ray showing deep brain stimulation hardware implanted in a patient. Figure 1A shows the extra-cranial components and 1B, the intracranial components. (1) pulse generator, (2) extension wire (3) deep brain stimulation lead (4) tip of the lead with four electrode contacts implanted in the target

only in around 1%–2% and mortality in <0.5%.[22] The complications of DBS are shown in Table 2. DBS improves motor fluctuations and the motor symptoms of PD, ability to perform activities of daily living and the QOL, and is avidly supported by evidence from more than half a dozen randomized controlled studies and numerous short- and intermediate-term (up to 5 years) observational studies. The long-term (8 years and beyond) follow-up studies published so far for subthalamic nucleus (STN) DBS have shown persisting benefits for cardinal motor symptoms such as tremor and rigidity, though axial functions (gait, balance, speech) worsen back to or below the baseline, attributable to the progression of neurodegeneration unaffected by the functional neurosurgical procedure. A detailed discussion on the indications, patient selection, surgical aspects, and programming of DBS is beyond the scope of this review, which will be focusing on the improvement of LID with surgical treatments.

Targets for Deep Brain Stimulation in Parkinson's Disease

The initial target tried for DBS in PD was the ventralis intermedius (VIM) nucleus of the thalamus, which resulted in significant tremor improvement.[21] However, VIM thalamus was soon replaced by other targets, particularly the STN and GPi, as the relief of other cardinal symptoms of PD was unsatisfactory with thalamic DBS.[23] Other newer targets explored for DBS in PD include the pedunculopontine nucleus for gait disturbances and freezing and the caudal zona incerta/posterior subthalamic area for tremor; these remain largely experimental at the moment.[24,25] The comparative efficacy and long-term safety of the two targets commonly used in clinical practice continues to be a matter of debate. Both targets have been found to be efficacious and safe. STN target allows higher reduction of medication doses compared to GPi and may be marginally better in improving the motor symptoms and ability to perform daily activities, while GPi target could have a marginal edge over its counterpart when neuropsychiatric and cognitive outcomes and improvement in QOL scores are considered.[26-29] However, cognitive and neuropsychiatric outcomes were not different between the two targets in the recent reports with longer follow-up, as well as a meta-analysis of randomized controlled trials.[30,31]

Table 1: Guidelines for selection of patients for deep brain stimulation for Parkinson's disease

General criteria	Factors favoring a good outcome
PD >4 years' duration	Good levodopa response (>50% improvement in UPDRS motor scores after standard dose of levodopa)
Presence of disabling motor fluctuations with or without disabling or dose-limiting LID	Absence of significant gait and axial impairment in the medication on state
Absence of "red flags" suggestive of the diagnosis of atypical parkinsonian syndromes	Absence of clinically significant cognitive dysfunction, active neuropsychiatric comorbidities (depression, psychosis) or behavioral disturbances
	Younger age (<70 years)
	Good social support; ability to come for regular follow-up
	Absence of poorly controlled medical/surgical comorbidities

UPDRS = Unified Parkinson's Disease Rating Scale, LID = Levodopa-induced dyskinesia, PD = Parkinson's disease

Table 2: Deep brain stimulation: Surgical and long-term adverse effects

Surgical/hardware-related complications	Other adverse effects
Intracerebral hemorrhage	Dysarthria
Pneumocephalus, seizures	Reduced verbal fluency
Venous infarcts	Mild (often clinically insignificant) changes in memory and executive functions
Anesthetic complications	Apraxia of eyelid opening
Deep vein thrombosis, pulmonary embolism, Postoperative atelectasis	Mood changes, impulse control disorder, probable increased risk of suicide
Wound/implant infections	Weight gain
Lead malpositioning/dislocation/fracture	
Postoperative delirium	

Subthalamic nucleus

STN is currently the most common target for DBS in PD across the world; GPi is considered by most centers as an alternative when there are clear contraindications for STN implantation.[32] The dorsolateral STN, located 1–3 mm posterior, 9–12 mm lateral, and 4–5 mm inferior to the line joining the anterior and posterior commissures (mid commissural point), is the typical target[33] [Figure 2]. STN DBS results in stable improvement of the cardinal motor symptoms of PD for many years though studies with follow-up more than 5 years have shown decline in axial motor functions and QOL, resulting from the natural progression of PD.[34-42] STN DBS offers a sustained improvement of LID. The remarkable improvement of LID following STN DBS is largely attributable to the reduction in the levodopa equivalent daily dosages (LEDDs) allowed by the robust improvement of motor symptoms provided by DBS. An average 50%–60% reduction in the dose of dopaminergic

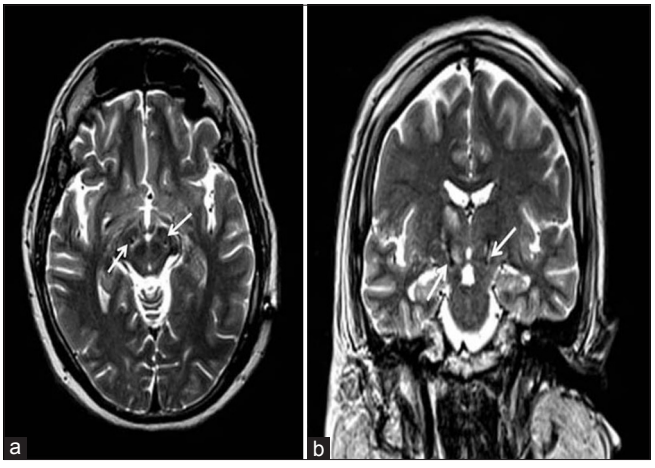

Figure 2: Postoperative magnetic resonance imaging scan showing deep brain stimulation lead implanted in the subthalamic nuclei. (a) Axial section (b) coronal section. Arrows point to the implanted lead tips

medications is possible after successful programming of DBS, with a mean reduction of dyskinesia scores by around 60%–70%. The reduced LEDDs remain stable in the initial 5 years in most studies, with a parallel stable control of LID; the improvement in dyskinesia scores persisted even after a decade in some of the long-term follow-up studies.[39,40] Conversely, increase in LEDD back to original levels in an attempt to control the stimulation-refractory axial motor symptoms has been shown to result in a parallel worsening of LID, supporting the view that the major contributor to control of LID in the long term after STN DBS is medication reduction.[42]

The possibility of a direct antidyskinetic effect of STN stimulation has also been pointed out by some studies. Off-period dystonia improves markedly with STN stimulation; it has been shown that 30%–50% reduction of diphasic/peak dose dyskinesia also occurs in patients with STN DBS even when challenged with preoperative doses of medications. Thus, the antidyskinetic property of STN DBS stems from more than one factor, with a major contribution from medication reduction and an additional, possible direct antidyskinetic effect.[18,43,44]

Globus pallidus internus

The GPi target is located approximately 2 mm anterior and 5 mm inferior to the mid-commissural point and 17.5–19 mm lateral to the third ventricular wall[33] [Figure 3]. The postero-ventral GPi is targeted, slightly anterior and lateral to the target usually used in pallidotomy. The motor improvement in the initial years after surgery is similar to that achieved by STN DBS.[29] The long-term outcome after GPi DBS for PD is less clear than the STN target; compared to the reports on STN target, there have been fewer long-term observational studies for the GPi target, and studies beyond 6 years of follow-up are currently unavailable.[22] GPi DBS allows only a lesser degree of reduction of dopaminergic medications; available reports also suggest that the stability of improvement of motor functions and motor fluctuations with GPi DBS over the years may not be as good as that reported with STN DBS.[30,32,45,46] In spite of this, the control of LID achieved with GPi DBS remains stable, clearly indicating a direct antidyskinetic effect of this target.[26,45] Most studies have shown a sustained and stable improvement of dyskinesia scores by around 60%–70% with the GPi target.[29,30,45,46]

The choice of the DBS target should be individualized; the patient's clinical profile as well as the experience and comfort of the movement disorder surgical team are equally important in this decision. Patients who have LID as the most dominant clinical problem and who otherwise tolerate levodopa well and therefore do not want a major dose reduction if LID can be controlled are the ones who could be considered for GPi DBS.[43]

Lesioning Surgeries

Several studies published in the 1990s showed the efficacy and safety of unilateral pallidotomy in the treatment of PD and ushered the postlevodopa era resurgence of the interest in pallidotomy.[47-50] The procedure is commonly done using MR-based stereotaxy. Intraoperative macrostimulation and assessment of benefits and adverse effects are used to ensure correct targeting; after confirming efficacious and safe targeting, thermal lesions are generated at three or four points along the track to create a cylindrical lesion in the postero-ventral GPi[50] [Figure 4]. The radiofrequency lesioning is relatively safe; partial visual field defects and cortico-spinal deficits such as dysarthria, facial weakness, hemiparesis, and dysphagia are the common adverse effects described. Even though they could occur in around 20% of the cases overall, they are transient and disappear after a few months in at least half of the instances.[51] Serious adverse events such as intracerebral hemorrhage are rare.

A striking 70%–90% improvement in contralateral dyskinesia and a less robust (around 50%) improvement of ipsilateral dyskinesia are achieved after pallidotomy. This is also accompanied by a modest improvement of contralateral parkinsonian signs. The benefit for ipsilateral and axial LID tends to wane off with time. However, the improvement of contralateral LID, the most stable benefit with pallidotomy, may

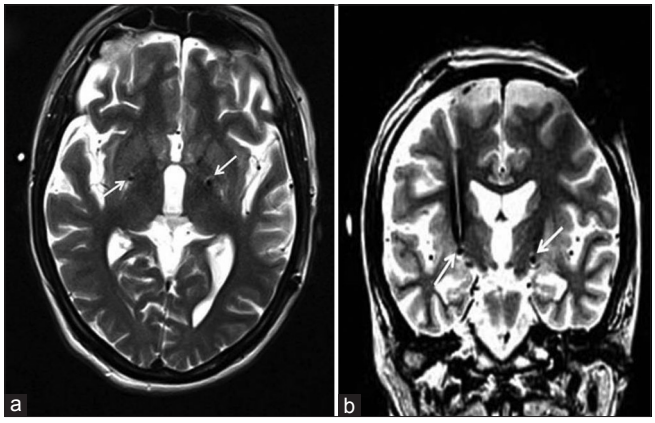

Figure 3: Postoperative magnetic resonance imaging scan showing deep brain stimulation leads implanted in the internal globus pallidus. (a) Axial section (b) coronal section. Arrows point to the implanted lead tips

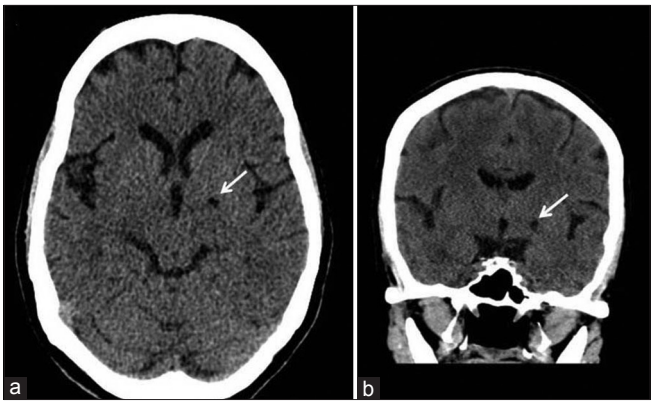

Figure 4: Postoperative computed tomography scan of a patient with Parkinson's disease who underwent left pallidotomy. (a) Axial image (b) coronal reconstruction. Arrow points to the surgically created lesion

persist even after 10 years.[52-54] Benefit for tremor also tends to persist while that for rigidity and bradykinesia usually wanes off. Randomized controlled trials have shown superiority of unilateral pallidotomy over best medical treatment for control of parkinsonian symptoms and LID. However, unilateral pallidotomy is inferior to bilateral STN DBS in controlling parkinsonian motor symptoms, improving daily activities, and reducing the dose of dopaminergic medications.[55,56]

Pallidotomy is considered to have effects very similar to unilateral GPi DBS with regard to improvement of LID and motor signs.[22] Pallidotomy and STN DBS provide similar degree of control of LID; however, STN DBS improves parkinsonian motor signs in off as well as on medication stage to a better degree than pallidotomy.[18] The major limitation of pallidotomy is the concern regarding clinically significant adverse effects, particularly cognitive dysfunction and cortico-bulbar dysfunction, when performed bilaterally.[57,58] Remarkable reduction in medication doses is not achieved with pallidotomy. Axial motor dysfunction, including freezing of gait and postural instability, does not improve with the procedure. In spite of these limitations, pallidotomy continues to have a role in patients with disabling motor complications, particularly LID, when DBS is not feasible for various reasons. DBS needs lifelong specialized care with special precautions during surgical and radiological procedures and regular follow-up assessments for programming aimed at relief of worsening or new symptoms. Monitoring of the IPG battery status is also important; inadvertent battery drain and the resulting abrupt cessation of stimulation could lead to acute severe worsening of parkinsonism and related complications. DBS is a costly procedure and demands recurring costs for periodic replacements of the IPG. Thus, pallidotomy is a viable option even in the DBS era when concerns on affordability of DBS and feasibility of having regular follow-up visits exist, particularly in the developing world where medical insurance coverage and accessibility to highly specialized services are limited. Pallidotomy is safer in those with significant medical comorbidities where risks of general anesthesia are high, or in whom implant surgeries are risky, like immunocompromised individuals.[51]

Magnetic Resonance-guided Focused Ultrasound Pallidotomy

A remarkable advancement in the field of ablative procedures is "incisionless" stereotactic magnetic resonance (MR)-guided focused ultrasound lesioning, which is less invasive than the conventional radiofrequency ablation.[59] The ultrasound device used consists of an array of transducers placed like a helmet delivering focused ultrasound through the skull to small volumes of deeply placed target brain tissue. The ultrasound device and the accessories are integrated into an MR scanner for MR guidance to focus sonication of the target area. Assessment of skull thickness using computed tomography scan is done prior to the procedure to tailor the therapy for individual patients. The focused ultrasound results in rapid rises in temperature in the defined target tissue volume. The acoustic power can be increased in a step-wise manner to reach the typical ablation temperature.[60] Preliminary reports of the efficacy of ablative procedures in essential tremor (ET) and PD are encouraging.[59,61,62] A recently published randomized controlled trial reported persisting benefits in ET patients who underwent ultrasound thalamotomy (compared to those who underwent sham procedure) 12 months after the procedure, though around 20% had persisting adverse effects (gait/sensory disturbances).[63] Several Phase 1 trials of pallidotomy using this technique to control dyskinesia in PD are ongoing.[60] With further refinements of the techniques, MR-guided focused ultrasound pallidotomy may emerge as a less invasive option compared to the conventional radiofrequency ablation.[61,64] However, more experience and evidence on efficacy and safety from systematically conducted studies is needed to recommend this technique over established methods, in routine clinical practice.

A comparison of STN DBS, GPi DBS, and pallidotomy in PD is presented in Table 3. Other lesioning surgeries practiced in the past, such as thalamotomy and subthalamotomy, are rarely done for control of LID in the current era because of concerns regarding efficacy and safety.[51]

Surgical Treatment of Levodopa-induced Dyskinesia - Underlying Mechanisms

The classical model of the basal ganglia describes the cortico-striatal activity channeled to GPi, the major basal ganglia output nucleus, through two parallel pathways - the "direct" pathway (striatum to GPi) and the "indirect" pathway (striatum to globus pallidus pars externa [GPe], GPe to STN, and STN to GPi). The GPi inhibits the thalamo-cortical projections. The direct pathway, by inhibiting the GPi, facilitates thalamo-cortical excitation while the indirect pathway excites the GPi and leads to inhibition of thalamo-cortical activity. Deficiency of dopamine renders the direct pathway hypoactive and the indirect pathway hyperactive, leading to hyperactivity of GPi and inhibition of thalamo-cortical activity resulting in parkinsonian state. Conversely, GPi activity is suppressed in the dyskinetic state.[65,66]

Though this classical model provides a conceptual framework for understanding the pathophysiology of many movement disorders, its limitations are also evident from several laboratory studies and observations in patients. Worsening of parkinsonism is expected with lesioning of motor thalamus in this model, which does not happen in reality. Similarly, lesions of GPi are expected to relieve parkinsonism and worsen dyskinesia. However, pallidotomy results in a dramatic improvement of LID, paradoxical to the worsening expected.[66,67] Based on several studies including observation of local field potentials and computational models, it is currently believed that, rather than rate of firing, pathological alterations in the pattern of firing are more important in the

Table 3: Comparison of subthalamic nucleus and internal globus pallidus deep brain stimulation and pallidotomy

	STN DBS	GPi DBS	Pallidotomy
Indications	PD with levodopa-responsive motor symptoms and motor fluctuations with or without LID or poorly levodopa-responsive PD tremor. Preserved cognition; no active psychiatric symptoms	PD with levodopa-responsive motor symptoms, motor fluctuations and LID. Preserved cognition; no active psychiatric symptoms	PD with disabling LID which is predominantly unilateral. Preserved cognition; no active psychiatric symptoms
Laterality	Can be safely done bilaterally	Same as STN DBS	Bilateral procedures are associated with unacceptable cognitive/pseudobulbar side effects
Surgical technique	Prolonged procedure involving both awake stereotaxy for lead placement and GA for IPG implantation. Awake stereotaxy needs patient's co-operation	Similar to STN DBS; technically easier than STN DBS	Much shorter procedure. Awake stereotaxy; needs patient's co-operation. No need of GA and more suited for those with major medical comorbidities
Surgical complications	Intracerebral hemorrhage; anesthetic complications, implant infections, lead fracture, and other hardware complications. Stimulation-related side effects are manageable by programming	Same as STN DBS	Corticospinal side effects; visual field defects. May persist. No implant/hardware-related complications
Effect on parkinsonian symptoms and signs	Excellent improvement of tremor, rigidity, and bradykinesia, persisting even after 10 years. Moderate improvement of gait and other axial symptoms; the improvement of axial functions wanes off after the initial few years	Similar/marginally lesser improvement compared to STN DBS. Long-term (beyond 5-6 years) outcome less clear	Improvement of contralateral parkinsonian signs. Axial signs do not improve. Improvement of tremor tends to persist while that of rigidity and bradykinesia may not be sustained over the years
Effect on LEDD	Significant reduction (50%-60%) in LEDD is often possible post-DBS	Only mild reduction in LEDD is possible	No reduction in LEDD
Antidyskinetic effect	Mainly attributable to medication reduction allowed by improvement of parkinsonism. Sustained improvement of LID even after 10 years	Robust and sustained direct antidyskinetic effect	Robust direct antidyskinetic effect on contralateral dyskinesias; persists even after 10 years. Transient benefit for ipsilateral and axial dyskinesias
Potential to modify therapy	New/worsening symptoms and adverse effects potentially manageable by programming of DBS	Same as STN DBS	No further adjustments are possible once lesion is created
Cost	Expensive. Recurring expenses for periodical pulse generator replacements	Same as STN DBS	Much less expensive than DBS; no recurring expenses
Follow-up	The implanted pulse generator necessitates meticulous follow-up and specialized care	Same as STN DBS	No implants; suitable for patients in whom follow-up with specialized centers is not feasible

STN = Subthalamic nucleus, GPi = Globus pallidus internus, DBS = Deep brain stimulation, LEDD = Levodopa equivalent daily dose, LID = Levodopa-induced dyskinesia, PD = Parkinson's disease, GA = General anesthesia, IPG= Implanted pulse generator

genesis of LID. The disorganized pattern of activity in the GPi and subsequent changes in the oscillatory activity in basal ganglia circuits underlie LID; this explains the improvement with lesioning of GPi.[68,69]

The clinical effects observed with DBS are very similar to those with lesioning surgeries. This led to the hypothesis that DBS results in inhibition of the target nuclei; activation of presynaptic inhibitory axon terminals was implicated to be responsible for this. However, intraoperative recordings from the nuclei downstream and functional imaging studies were not supportive of suppression of activity in the target. It is currently believed that DBS overrides the disorganized and irregular bursting activity in the target nuclei and replaces it with a stimulation-induced, regular firing. As a result, the pathological low-frequency oscillations in the downstream basal ganglia networks are replaced by high-frequency regularized patterns.[70]

Future Prospects

Novel targets such as the centromedian/parafascicular nucleus of thalamus and the caudal zone incerta are being explored for treating motor complications of PD. Neurostimulation for PD is witnessing several technological advances including robot-assisted DBS and use of intraoperative magnetic resonance imaging. Conventional cylindrical electrodes currently in use stimulate neurons around the entire circumference of the lead. Directional DBS leads are currently under trial. These carry radially segmented electrodes capable of delivering stimulation in directions orthogonal to the lead. These could theoretically deliver more focused stimulation, minimizing stimulation-related adverse effects.[71] Closed-loop neurostimulation (adaptive DBS) is another evolving concept. In this, local field potentials recorded by the implanted electrodes themselves provide an ongoing feedback to regulate current delivery.

The current era is also witnessing a fascinating resurrection of the interest in neurorestorative therapies in PD, which had faced a setback following discouraging results from the initial trials of human embryonic mesencephalic transplants.[72,73] In spite of improvement in imaging markers of nigrostriatal dopaminergic innervation in many participants, overall improvement in motor functions, particularly in the older

patients and those with more advanced disease, was not satisfactory. Graft-induced dyskinesias, concerns on tumorigenesis and spread of alpha-synuclein pathology to grafted tissue, practical difficulties in the procurement of donor tissue, and importantly, ethical concerns contributed to the initial desperation. With better understanding of the underlying neurobiology and refined protocols, newer clinical trials have been initiated recently.[74] Newer sources of stem cells, like parthenogenetic stem cells (derived from unfertilized oocytes) or autologous mesenchymal-derived stem cells devoid of ethical concerns, offering additional advantages such as lesser risk of teratoma formation and rejection and wider availability are also evolving.[75,76] Disease progression and degree of neurodegeneration being one of the major determinants of LID, these neurorestorative therapies could be a viable option to treat LIDs in the future.

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Conflicts of interest

There are no conflicts of interest.

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