DOI: https://doi.org/10.47391/JPMA.879

Deep brain stimulation for Parkinson's disease in Pakistan: current status, opportunities and challenges

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Abstract

Parkinson's disease is a slowly progressive neurodegenerative disease that commonly affects people aged 60 years and above. So far, no treatment has been shown to halt or slow the progression of the disease and our options are limited to symptomatic management. Levodopa is the most preferred antiparkinsonian medication that provides excellent control of symptoms early in the disease. However, in most patients the response declines over time and complications of motor fluctuations and dyskinesia arise. Other medical therapies play an adjunctive role in the management, as they are not as effective as levodopa. Advanced therapies like deep brain stimulation (DBS) can provide effective control of symptoms in moderate to advanced disease. Deep brain stimulation surgery has recently been started in Pakistan. This review provides an overview of deep brain stimulation, its indications, patient selection process and details of surgery, expected benefits and limitations as well as its history and challenges in Pakistan.

Keyword: Deep brain stimulation, Parkinson disease, Pakistan

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, with a median age-standardized annual incidence rate of 14 per 100,000 people in high-income countries(1). The lifetime risk is estimated to be 2% for men and 1.3% for women aged 40 years in the USA(1). PD incidence increases with

age so as the life expectancy increases it becomes more prevalent. PD is characterized by motor symptoms (mainly rest tremor, rigidity, bradykinesia and postural instability) and non-motor symptoms (including but not limited to depression, constipation, sleep problems, hyposmia and cognitive changes).

James Parkinson first described the disease in 1817 and Jean-Martin Charcot popularized it in his famous lecture in 1888(2), but effective treatment options were not discovered until 1950s. Before the discovery of levodopa, neurosurgeons lesioned various structures ranging from the cortex to the pyramids. Although they did enjoy success in alleviating the tremor, many patients were left with residual weakness. It was Meyers in 1940 who lesioned the head of the caudate nucleus and observed improvement in tremor without resultant hemiplegia(2). During the next two decades, surgeons improved the lesioning targets to primarily putamen and thalamus with success.

Soon after George Cotzias clearly demonstrated the benefit of levodopa in PD in 1968 (3) the horizon changed dramatically. Now we had a drug that could provide remarkable improvement in parkinsonian symptoms without the need of the surgery. This, understandably, put surgery for PD out of favour and the attention was shifted to medical management. However, it was Cotzias himself, who recognized the fluctuations in motor response to oral levodopa in PD in as early as 1971(4). We now believe that approximately 50-80% of the PD patients treated with levodopa for 5-10 years develop motor fluctuations, with wearing off of medication benefits within hours and medication induced dyskinesias at peak dose(5). Many patients with advanced PD, even on optimized medical therapy, spend a significant time of their day either being in an ‘off-state’ or with troublesome dyskinesia and some patients simply cannot tolerate medication.

This difficulty of managing a PD patient with motor fluctuations and dyskinesia coupled with a significant improvement in stereotactic surgical techniques owing to better neuroimaging by CT and MRI lead to a resurgence of surgical treatment for PD in the 1980s(2, 6). However lesioning of the brain was limited by various factors including

most importantly permanent side effects, most notably dysarthria. This led Benabid and colleagues to consider Deep Brain stimulation as an alternative to lesioning surgery and documented success in 1987 initially on patients with unilateral thalamotomy and then surgery naïve patients, later shifting to Subthalamic Nucleus (STN) as the preferred target for PD by 1992(7, 8). With these techniques, we now had an opportunity by which parkinsonian symptoms could be controlled fairly consistently throughout the day and with a markedly reduced need for medications with less side effects. The magnitude of this benefit cannot be overstated and perhaps is the most important intervention in PD besides levodopa therapy.

DBS has now been performed in more than 150,000 patients with movement disorders and more than 700 centers in the world practice DBS surgery for PD(2). DBS for PD has recently been introduced in Pakistan with great success at Lahore General Hospital while other hospitals are following suit. This review will provide a brief introduction to DBS, followed by its technique, patient selection and challenges in Pakistan.

What is Deep Brain stimulation?

Deep brain stimulation (DBS) is an option that provides continuous electrical stimulation of one of the deep nuclei of the brain, for example thalamus. To perform the stimulation, a wire is implanted in the brain (Figure 2), with its tip being in the target nucleus, such as sub-thalamic nucleus (STN) or Globus pallidus interna (GPi) for PD. The conventional wire usually has four contacts (or terminals), which can be a positive or a negative terminal of an electrical circuit. The wire is then connected to an impulse generator (or stimulator) that is placed in the subcutaneous tissue in front of the chest and hooked up via connecting wires. These connecting wires travel subcutaneously from the site of the burr hole in the skull to the stimulator implanted in front of the chest, tunneling behind the ear under the skin.

How dose Brain stimulation work?

When stimulation is on, a current loop is created, from the negative terminal (or contact) on the lead to the positive one. Delivering electrical stimuli to the brain modulates or disrupts patterns of neuronal signaling adjacent to the region(9). Locally, the neuronal

cell bodies are inhibited, and nearby axons are stimulated. This results in altered firing patterns of these neurons and hence disrupts the thalamo-cortical circuits and other pathways (9) which reduces tremor.

Other effects of DBS have also been described. Neurotransmitters such as adenosine and glutamate are released (10) from neighbouring astrocytes. There is also evidence that the blood flow is increased and neurogenesis is enhanced(11). However, the precise mechanism(s) how these are beneficial in PD is not known.

Pre-surgical aspects of DBS

Which PD patient will benefit from DBS?

Patient selection is the most important factor that determines outcome of DBS. DBS DOES NOT affect disease progression of PD and DOES NOT improve all aspects of PD. And only about 5-10% of the patients with PD in the best centers of the world are candidates for DBS. It is easy to have failure of therapy or even worsening of symptoms in poorly selected patients.

The characteristics of the PD patient that make him/her a good candidate for DBS surgery include(9): adequate response to dopaminergic therapy, presence of on-off fluctuations, dyskinesia impairing quality of life, medication-resistant tremor and reasonable cognitive function.

Factors that predict poor response to DBS include dementia, unstable psychiatric disease, severe autonomic and gait dysfunction and most importantly atypical parkinsonism (progressive supra-nuclear palsy, multiple system atrophy, cortico-basal ganglionic degeneration, dementia with Lewy bodies). DBS has not been convincingly shown to benefit patients with atypical parkinsonism(9).

What benefits can be expected from DBS?

Even in properly selected cases, it is very important to be exactly clear and educate patients on what benefits are we expecting and what will not get better or may even get worse after DBS. The patient and any family members involved in the decision making must be perfectly clear on these aspects and have reasonable expectations and awareness of complications.

A useful point to remember is that, "What gets better with levodopa gets better with DBS". Each symptom of PD, whether motor or non-motor, has a different success rate with DBS. Tremor, for example, gets completely alleviated in 80% of cases and gets partially improved in most of the rest. There definitely are symptoms that don't get better with DBS. Dysarthria and postural instability don't improve with DBS and may even worsen with STN DBS(12). Therefore, it is imperative to have a detailed discussion with the patient about what benefits he/she wants. For instance, if the benefits that they are looking for are more of an improvement in balance and falls, then DBS might simply not be for them.

How do we select the right patient for DBS?

The best place to start is a Movement Disorders Neurologist consultation to ascertain as best as possible the diagnosis of Idiopathic Parkinson's Disease and rule out atypical and drug induced parkinsonism. As idiopathic PD is still a clinical diagnosis, proper training and experience of neurologists is critical. Figure 2 summarizes the important steps in the patient selection process.

The expert also evaluates indications and contraindications of DBS, patient goals are reviewed and realistic outcomes for DBS surgery are discussed. The decision is made regarding candidacy to pre-op evaluation including a challenge dose of levodopa.

Each patient undergoes a formal outpatient neuropsychological evaluation. The goals are to rule out cognitive impairment in general, and verbal fluency testing is perhaps the most important aspect as DBS can adversely affect speech. Dementia Rating Scale scores of more than 130/144 are typically required to proceed with the surgery(13).

An MRI brain (at least 1.5 Tesla) with thin sections through the basal ganglia is obtained to rule out contraindications like structural lesions and findings of atypical parkinsonism etc. and is used for imaging-based targeting. Dopamine Transporter Scan (DaT scan) may be considered if the diagnosis is in doubt but is not yet available in Pakistan.

A formal On/OFF testing is completed as described (13) with formal Unified Parkinson Disease Rating Scale (UPDRS) scores and gait testing. An improvement of 30-50% or

more in the motor component (part 3) of UPDRS has been used in studies as a criterion for patient selection.

The complete case, starting from history, examination, evaluation findings and patient goals, is reviewed by a DBS team that includes movement disorder neurologist, neurosurgeon, physical therapist, occupational therapist, speech therapist and psychologist for a final recommendation and target selection for the patient.

Where should the DBS wire be placed?

Although more and more targets are being explored, the two leading targets that have shown clear efficacy in controlling the motor symptoms in PD are subthalamic nucleus (STN) and globus pallidus interna (GPi). **Error! Reference source not found.** compares these two with VIM (ventral intermediate nucleus) of thalamus for PD. Although both STN and GPi stimulation have been shown to be equally efficacious in controlling PD motor symptoms (14) there are clear differences and one might be better than the other in selected cases. As an example, STN stimulation leads to more reduction in medication need while GPi stimulation causes more dyskinesia suppression. Similarly, GPi may have less concern for cognitive and mood problems. Additionaly, there are practical differences in programming these targets after surgery.

Surgical Aspects of DBS

DBS Surgery

DBS surgery is performed in two stages. The patient is awake, under local anesthesia, during the first stage when the DBS wires are being implanted into the target nucleus. The second stage of placing the stimulator battery requires general anaesthesia.

The key aspect of surgery is the proper placement of the tip of the lead with 1 mm accuracy into the target nucleus. However anatomical targeting currently does not correlate with the physiological function of the nuclei and thus good placement is achieved in three ways:

First, using *Imaging guidance* with either visible markers of target or more commonly using standard distance from the midpoint in brain for a given target.

Second, by *Microelectrode recording* (MER) during the awake surgery. Each nucleus of the brain has its own firing pattern and by recording the electrical stimuli from various structures with the help of a micro-electrode, experts can recognize the patterns.

Third, using *Macrostimulation* by clinical examination during the surgery. After placing the actual DBS lead, it is stimulated to look for improvement in parkinsonian symptoms, and very importantly any side effects of stimulation that may be seen due to spilling of the electrical stimulation into the neighborhood structures that may cause effects like eye deviation, sensory dysesthesia, muscle spasms and pulling. This allows for instant revision of placement in the surgery.

Complications of DBS Surgery

Short term complications of DBS Surgery

The most serious complication is rupturing a blood vessel and creating a haematoma, the chances of which are about 0.5% with risk of death of about 50% of the ones that bleed. The most common serious complication is surgical site infection that may require removal of the implanted leads, neuro-stimulator or both. Other adverse events include device-related complications such as lead migration and defective lead wires, seizures, headache, confusion and poor wound healing. Goodman et al. studied 100 patients implanted with a total of 191 STN devices and found that there were 7 (3.7%) device infections, 1 cerebral infarct, 1 intracerebral haematoma, 1 subdural haematoma, 2 (1%) skin erosions, 3 (1.6%) periprocedural seizures, and 6 (3.1%) brain electrode revisions. There were no surgical deaths or permanent new neurologic deficits (15, 16). Generally, most serious adverse events however, do resolve in 99% of cases by 6 months (17). STN stimulation may produce ballistic and choreic dyskinesia when the voltage is increased above a given threshold (16, 18).

Long term complications of DBS Surgery

A variety of long term complications of DBS Surgery have been reported. Some are stimulation related and hence are amenable to improvement by changing the programming parameters (see “What is DBS Programming” below for a discussion of programming parameters). Kenney et al. published the safety outcomes of 319 patients

who underwent DBS implantation at Baylor College of Medicine, Houston, Texas over a 10-year period. Of these, 182 patients had PD and 113 had essential tremor. Long-term complications of DBS surgery included dysarthria (4.0%), worsening gait (3.7%), cognitive decline (4.0%), and infection (4.4%) (16, 19).

In one controlled study, 60 patients were randomly assigned to receive STN DBS and 63 to have best medical treatment. After 6 months, DBS-treated patients showed mild but significantly more evidence of impairments in executive function and verbal fluency, irrespective of the improvement in quality of life. In contrast, anxiety was reduced in the DBS group compared with the medication group (20). Another meta-analysis revealed that a decrement in verbal fluency was the most common cognitive side effect of DBS (9, 21). This is an effect of surgical electrode implantation, not an effect of stimulation (9, 22). In another study of 60 patients who underwent 96 DBS-related procedures, followed over a period of 43.7 months (range 6–78 months), 18 (30%) developed 28 adverse events, requiring 28 electrodes to be replaced (16, 23).

Post-Surgical Aspects of DBS

When to start DBS Programming?

Different centers have different protocols on when to start the stimulation and no consensus guidelines exist. Many centers wait up to 4-6 weeks, for the wound to heal and more importantly, for the so called ‘lesioning-effect’ to subside before turning on the DBS. Lesioning effect is the phenomenon of transient improvement in parkinsonian symptoms due to the effects of the surgery and the intraoperative microelectrode stimulations. This transient improvement can last days or even weeks. However, some centers turn on the DBS as soon as the next day.

What is DBS Programming?

One of the two major advantages of DBS over lesioning surgery is the ability to choose between thousands of settings of stimulation. Finding the right setting of the DBS requires considerable training and experience. There are a lot of different options to set the stimulation parameters.

First, as mentioned above, each lead has four contacts, that can all be set to be positive or negative, singly or in combination. Other parameters include voltage (0-5 V), current (milliamperes, mA), frequency (ranging from 30-450 Hz) and pulse width (ranging from 60-280 microseconds). A combination of any of the above point within the range is possible giving rise to more than 6500 potential combinations. Formal algorithms do not currently exist and the approach is individualized for each patient by the movement disorder neurologist based on known evidence.

The battery can last anywhere between 3-5 years depending upon the stimulation settings. Setting it to deliver higher voltages will drain the battery faster. Batteries are usually checked every 6 months and it is recommended to change them once they are below certain threshold (different for each device). The battery changing process is fairly straightforward as the lead placement in the brain is permanent.

Can DBS be used for other reasons?

Reviewing all the known and approved indications for DBS are beyond the scope of this review but briefly, DBS is approved for use in essential tremor and generalized dystonia and is well established for focal cervical dystonia, obsessive compulsive behaviours in Tourette's syndrome and intractable epilepsy and likely beneficial for resistant depression.

Limitations of DBS?

The most important point to remember and keep reminding the patient is that PD is a progressive disease and DBS 'DOES NOT' slow the progression of the disease. However, it can be reprogrammed to control advancing or newly appearing symptoms. Often patients feel that the DBS has stopped working as they are noticing reemergence of symptoms. An easy way to tell is by turning off the DBS device and seeing if the symptoms get worse or not. Most times they do and what the patient actually needs is changes in the DBS settings to hopefully take care of the symptoms.

The most important reason for failure of DBS is a non-ideal initial DBS candidate. Therefore, adequate multidisciplinary team for patient selection as well as long term

care and clearly defined expectations are critical to the optimal response to DBS and to prevent potential "DBS failures" (Okun et al., 2008).

Establishing DBS in Pakistan

Current State of DBS in Pakistan

Lesioning surgery for tremors and Parkinson's Disease was adapted very early in Pakistan pioneered by the late Prof Bashir Ahmed. (http://www.pulsepakistan.com/index.php/main-news-dec-1-15/1404-prof-bashir-ahmad-mbbs-frcs). However, adaption of DBS in Pakistan has been delayed due to a combination of factors including cost of therapy, lack of expertise and training and barriers to find training programmes internationally.

DBS in Pakistan was originally introduced in 2014 at Lahore General Hospital (https://www.dawn.com/news/1141942) with minimal resources. Despite initial challenges of surgical complications, some good results were achieved soon afterwards and more than 20 patients received the therapy with Medtronic Activa system (http://dbspakistan.com/faq.html). Formal analysis of outcomes of these initial cases has not been published to best of our knowledge but was presented at local meetings and proceedings. The next breakthrough of DBS in Pakistan came in 2018 when 6 cases were implanted with Abbot Infinity DBS device system at Lahore General Hospital and Bahria International Hospital Lahore.

More recently DBS surgery has been provided at other institutions within Pakistan; making the total number of centers with ability to offer the surgery to five. Nearly 40 patients have received the surgery within the country. (authors personal correspondence, unpublished data) A great effort has been initiated in neurosurgery to make DBS expertise more available in Pakistan.

Challenges of DBS in Pakistan

Patients seeking advanced therapies for their disabling conditions have often traveled to India, Germany, Middle east and even the United States to receive the surgery with proper screening before the surgery. However, no formal or convenient structure exists to provide them follow up and programming or even troubleshooting for the device.

Currently there is no fellowship trained Movement Disorder (MD) neurologist practicing in Pakistan.

Fortunately, recent surgical advances in DBS have been paralleled with similar development in MD neurology. Pakistani-US MD neurologists have partnered with Pakistan Society of Neurology to offer multiple educational programmes including conferences, workshops and now an online mini-fellowship. This has significantly raised awareness and understanding of DBS among the neurology community to provide basic patient education and possibly selection. However much more formal training is required to offer DBS programming and electrophysiology. Again, this gap is being bridged by author DB frequent visit to Pakistan to provide direct patient care for these niches and few Pakistani Neurologist have been accepted for MD fellowship abroad with hope to bring back the expertise to Pakistan.

Besides expertise, cost remains a big challenge. Although the cost in Pakistan from 2-3 Million PKR is much lower than costs in India (5 Million PKR) and US (8-10 Million PKR), it is still a huge economic burden for most patients in Pakistan. This has generated interest in Chinese DBS programme (PINS) which if reliable could be a relatively lower cost offer and more importantly lesional surgery has not lost its place in terms of cost effectiveness, which if performed in carefully selected patients can still be a very good alternative to DBS and should be frequently used for cost reasons albeit with similar close MD neurologist collaboration for patient selection.

Conclusion

We live in an era in which more and more advanced therapies are emerging and being refined to improve care and quality of life of our PD patients. It is important to realize the indications, benefits and limitations of these techniques to properly educate our patients and provide them with practical options. DBS is a powerful technique that can bring a dramatic change in the quality of life of carefully selected patients with PD. No good database of the cases or their outcome currently exist and we may benefit from a National DBS patient Registry to improve the process of providing this surgical therapy.

Disclaimer: None to declared.

Conflict of Interest: None to declared.

Funding Sources: None to declared.

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393 **Table 1: Comparison of Targets for DBS in Parkinson's disease**

	STN Sub-thalamic nucleus	GPi Globus pallidus interna	VIM Ventral intermediate nucleus of thalamus
Motor Control	Improved UPDRS motor score. Increased ON time without dyskinesia Reduced OFF time	Improved UPDRS motor score. Increased ON time without dyskinesia Reduced OFF time	Tremor control only. No effect on bradykinesia or rigidity
Medication Dosage	More reduction in medication need (50-100%)	Typically no change in medication, but improves tolerance due to dyskinesia suppression	May reduce medication need
Dyskinesia	May directly suppress dyskinesia but not as much as GPi. Most dyskinesia suppression is achieved due to reduced medication need	Actively suppresses dyskinesia.	No direct effect, but may reduce owing to lesser medication need

Gait	May improve freezing. May worsen gait or falls	No negative effect. May improve freezing	No definite effect. May increase falls
Cognition	Worsens. Especially verbal fluency and processing speed	Less or no effect on cognition	No known effect
Mood	Concern for worsening depression. At least one suicide reported	Lesser concern for depression. Mood may even improve (14)	No concern
Surgical Mapping	Relatively easy to target and confirm by micro stimulation	Toughest target	Easiest target
Programming	Relatively easy to programme but requires multiple steps	Much harder to programme	Easy, quick and straightforward programming

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Figure 1: a) Coronal section and b) oblique through the brain showing the relationship of the DBS wire with basal ganglia

1 – Subthalamic nucleus, 2 – Red Nucleus, 3 – Substantia nigra, 4 – Ventral Intermediate nucleus of Thalamus (alternative target for tremor surgery), 5 – Globus Pallidus Interna (postero-caudal segment) (alternative target for PD surgery)

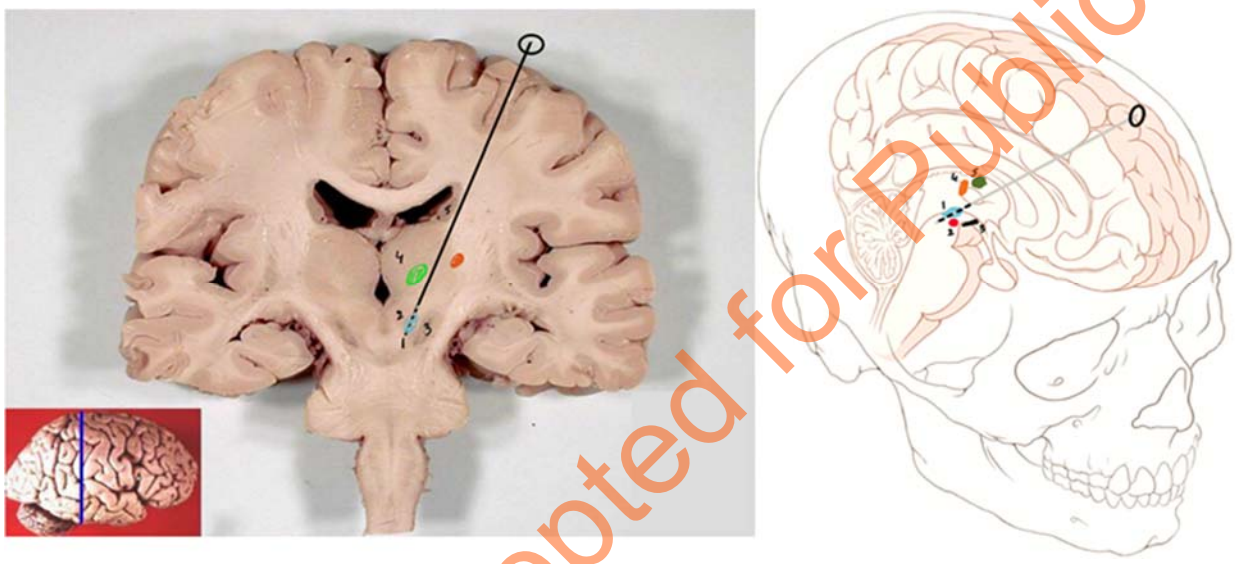
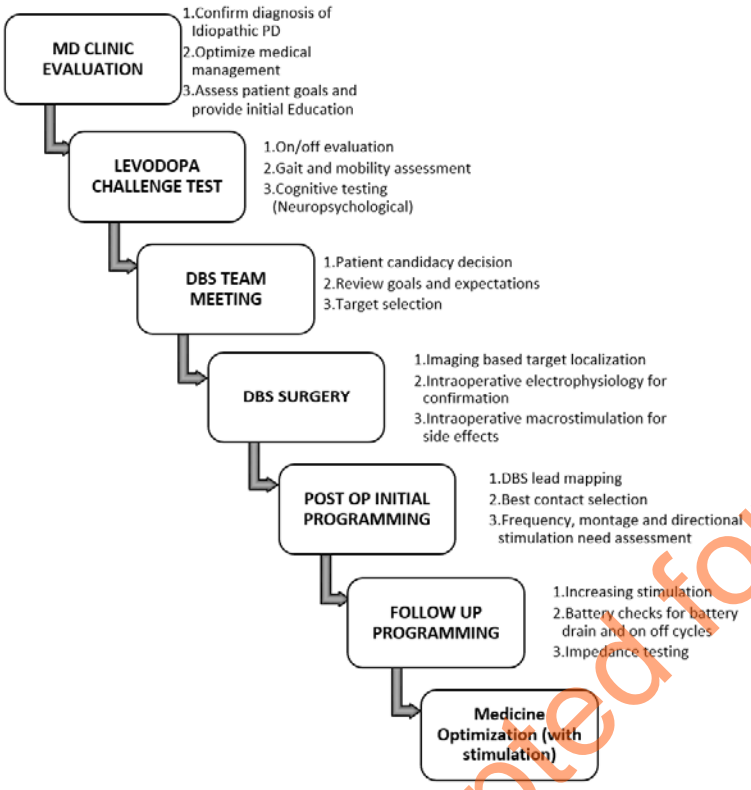


Figure 2: Surgery Process Flowchart -with key steps and measures needed at each step

MD – Movement Disorders

PD – Parkinson Disease

DBS – Deep brain stimulation



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