R E V I E W

Deep Brain Stimulation in Parkinson's Disease: Assessing Efficacy

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Abstract: Parkinson's disease (PD) has a chronic course. Currently, levodopa is the mainstay of treatment. However, long-term use of levodopa is interrupted by several side effects like dyskinesia and on–off fluctuations. Other pharmacological treatments also have adverse drug profiles and do not provide long-term relief, warranting the need for novel therapeutic approaches with a long-term efficacy profile in PD. Deep brain stimulation (DBS) is one such evolving technology with proven efficacy in advanced PD and promising results in early PD. DBS is mainly of two types, open- and closed-loop, of which open loop has been in routine use but closed loop is an innovative technology, only recently introduced for the treatment of PD. Apart from cost, DBS technology faces major challenges that hamper its integration into mainstream treatment paradigm of PD. Most of these challenges, including the cost can be overcome or considerably reduced by selecting the right DBS type, the right target for stimulation and the right patient selection. The review, therefore, assesses the efficacy of different parameters involved in selection of DBS as a treatment strategy such as patient characteristics, target characteristics, pros and cons of different DBS strategies, safety of DBS and stage of PD. The review may help clinicians to effectively use all these parameters to improve the outcomes of DBS.

Keywords: deep brain stimulation, Parkinson's disease, DBS in PD

Introduction

Parkinson's disease (PD), a chronic, progressive and debilitating neurodegenerative movement disorder, affects 1 to 2 per 1000 of the global population at any given point in time.[1] The prevalence of PD increases with age affecting approximately 1–3% of the global population aged 60 years and above.[1–3]

Currently levodopa is the mainstay of PD treatment.[4] However, long-term use of levodopa is interrupted by several side effects like dyskinesia and on-off fluctuations. Other pharmacological treatments like dopamine agonists, catechol-O-methyl transferase (COMT) inhibitors, monoamine oxidase (MAO) inhibitors, amantadine, anticholinergic drugs, etc. also have adverse drug profiles and do not provide long-term relief from symptoms.[4,5] Hence, patient's quality of life (QoL) progressively deteriorates.[4] Therefore, novel therapeutic efficacious approaches that improve patient's QoL are required.

Deep brain stimulation (DBS) is an effective treatment for PD. DBS is mainly of two types: Conventional or open loop (cDBS) and closed loop (CL-DBS) or adaptive DBS (aDBS). cDBS is routinely used in PD treatment but CL-DBS is an innovative technology, only recently introduced for the treatment of PD.[6]

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DBS has the potential to reduce motor and non-motor PD symptoms by 60–80%, with sustained reduction in medication use by 44% after 8 to 15 years of surgery.[7,8] Efficacy is achieved by modulating neural activity through a "brain pacemaker" implanted surgically for electrical stimulation to key brain structures, known as DBS targets.[9] Electrical stimulation can be modulated by changing frequency, pulse width and intensity to induce the desired clinical outcomes in PD.[9] Moreover, unlike surgical ablation, DBS can be performed bilaterally without major adverse effects.[9–12] High-frequency stimulation of brain targets has proven to be efficacious in the long run.[9] Also, patient satisfaction with the treatment and symptom control and ability to carry out activities of daily living (ADL) persists for a long time after DBS.[13] The efficacy and reversible nature of DBS along with the potential to significantly reduce the burden of drug therapy, has carved an important place for DBS in the long-term treatment of PD.[9]

However, despite its advantages, DBS is not a widely accepted technique; approximately only 2% of patients with PD undergo DBS. In many parts of the world, patients with PD have limited access to DBS; the treatment is costly and patients fear its invasive nature.[9] To improve patient outcomes in PD, it is very important to access the benefits of different DBS targets, devices and strategies and understand the patient characteristics that will improve DBS outcomes.

In this review, we elaborate on the efficacy of DBS in PD by understanding the role of effective patient, target and strategy selection. The review also covers upcoming technologies and their efficacy and ways to measure DBS efficacy. We also provide an overview of DBS efficacy in early versus advanced PD.

Literature Search Strategy

General literature search: a Google Scholar and PUBMED search was carried out from the year 2000 to 2020 by combining the following search terms using Boolean operators "AND/OR": "efficacy", "deep brain stimulation", "DBS", "Parkinson's disease", "DBS targets", "Subthalamic nucleus (STN)", "Internal globus pallidus (GPi), "Ventral intermediate nucleus (Vim)", "Pedunculopontine nucleus (PPN)", and "Posterior subthalamic area (PSA)". Studies demonstrating the efficacy of DBS in PD were included in the review. Only English language publications were considered.

Efficacy Measures

Several scales are used to assess the efficacy of DBS treatment in PD. Historically, scales like the Webster, Columbia University Rating Scale, and Parkinson's disease Impairment Scale had been developed to assess motor symptoms.[14] The Schwab and England and Northwestern University Disability Scale were developed to assess disability component. The Unified Parkinson's Disease Rating Scale (UPDRS) and New York University Scale were developed to assess both motor and disability components.[14]

However, of these, UPDRS (Table 1) became the most widely accepted tool. The UPDRS has four subscales: I to IV.[15–18] The UPDRS scale did not elaborate much on the non-motor symptoms and relied heavily on the patient/

Table 1 Unified Parkinson's Disease Rating Scale (UPDRS) and Movement Disorders Society Revision of UPDRS (MDS-UPDRS)

Subscale	Assessment Made (UPDRS)[15–18]	Assessment Made MDS-UPDRS[19,69]	Method of Assessing
I	Mentation, behavior, and mood	Non-motor Experiences of Daily Living	Data elicited from patient or caregiver; Reliability depends on patient/caregiver reporting and examiner's ability to elicit response.
II	Activities of daily living	Motor Experiences of Daily Living	Data elicited from patient or caregiver; Training tapes are available to improve reliability of measures
III	Clinician rated motor manifestations	Motor Examination	Examination based; Training tapes are available to improve reliability of measures
IV	Complications of therapy	Motor Complications	Data elicited from patient or caregiver; Reliability depends on patient/caregiver reporting and examiner's ability to elicit response.
Final scoring	Five response options: 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe		UPDRS: not an interval scale, not quantifiable; a score of 4 is not twice as severe as score of 2. MDS-UPDRS: scores have uniform anchors

caregiver's ability to report symptoms. Therefore the Movement Disorders Society revision of the UPDRS (MDS-UPDRS)[19] scale is currently used to assess improvement in DBS treatment.[20]

New efficacy measures are being explored to assess the efficacy of DBS. Dong et al (2020) explored whether Executive Control Network (ECN) could be used to assess the efficacy of DBS.[21] They found no difference in the functional connectivity (FC) of the ECN in PD before and after DBS. However FC to ECN differed between patients with PD and controls. The researchers concluded that ECN could be used to diagnose PD but not assess the efficacy of DBS.[21]

Patient Selection for Improved Efficacy

The efficacy of DBS depends on the expertise of the neurosurgery team[9] and on patient characteristics.[22,23] The "Core Assessment Program for Neurosurgical Interventions and Transplantation in Parkinson's Disease" (CAPSIT-PD) recommends that surgical intervention in PD should be considered in patients with disease duration of at least 5-years.[22] However, patients who are adequately controlled by medical management are not candidates for DBS.[23]

Patients should be critically chosen based on their symptoms, age and cognition status as the right patient selection increases the efficacy of DBS.[9] More than 30% of the DBS failures are because of improper patient selection.[23] Patients with non-motor symptoms (poor cognition, dysautonomia, postural instability, dysarthria, or dysphagia) not responsive to medication, also do not respond to DBS too.

The following patients on optimal drug therapy (ODT) are more likely to have good and sustained response to DBS if they have the following characteristics:[9,22,24] idiopathic PD/advanced PD; robust response to levodopa (>30% improvement in UPDRS III); ineffective management of symptoms with levodopa can increase risk of DBS rejection by 50%; experiencing complications to medical therapy (dyskinesias or motor fluctuations: significant off and on time); lack of significant psychiatric and/or mood symptoms; no history of dementia or depression; and <70 years old.

Unrealistic patient expectations should be addressed before DBS as these can reduce patient satisfaction and has shown to result in patients rejecting the effect of DBS

in 38% of cases.[24] Adding unrealistic expectations as a disqualifying criteria for patient selection for DBS can significantly improve patient selection for DBS.[24]

Effective Targets

Apart from patient selection, target selection is very important for effective and desired DBS outcome. Various DBS targets in the brain, STN, GPi, Vim, PPN, and PSA, have been effectively used and assessed to show improvement on the MDS-UPDRS scale (Table 2). Of these, STN DBS and STN GPi are the most commonly used and studied targets.[25,26] There is no consensus on the best target for DBS in PD.[26] Hence, DBS targets have to be chosen cautiously after assessing patient symptoms, age and cognitive status and role of the targets in improving symptoms and cognition (Table 2).[9,22]

Comparing STN DBS with GPi DBS

Sustained benefits of DBS of STN and GPi have been reported on motor function, motor fluctuations, dyskinesia and QoL.[27–30] Several studies have shown that STN DBS can reduce levodopa equivalent daily dose (LED) by 48% to >50%, 1 to 4 years post-surgery[31,32] STN DBS is more effective in reducing LED than GPi DBS.[33,34] Thomsen et al (2020) showed a reduction in medication use by 55% and 44% after 1 year and 8 to 15 years, respectively of STN DBS.[8]

Though both targets reduce levodopa induced dyskinesia (LID), GPi DBS is more effective in reducing LID than STN DBS (47–88% vs 20–83%, respectively).[35] Post DBS increase in levodopa dose results in higher rates of dyskinesia with STN DBS than GPi DBS.[27,36–39]

The two targets are comparable in improving rigidity and bradykinesia. A network meta-analysis of 16 studies looking at UPDRS improvement showed similar efficacy of GPi DBS (−3.9; 95% confidence interval [CI] −7.0 to −0.96) and STN DBS (−3.1; 95% −5.9 to −0.38) in improving UPDRS scores in the "on medication" phase.[26] Both the targets show similar effect on mood,[40] but GPi DBS is associated with lesser mood, cognition and behavior abnormalities than STN DBS.[25] A meta-analysis showed that STN DBS is associated with decreases in executive function, memory, attention, psychomotor speed and semantic and phonemic verbal fluency; while. GPi DBS showed small deficits only in verbal fluency and attention.[41] Though, patients report better QoL after both GPi DBS and STN DBS, the QoL after GPi DBS was significantly better (P = 0.03) than that post STN DBS on

Table 2 DBS Benefits on Different Targets

Target	Effect	Benefit of DBS (Conventional DBS Unless Specified)
Established targets		
Subthalamic nucleus (STN) and local fiber pathways	Suppress cardinal PD symptoms like bradykinesia, rigidity and tremor[9]	1. MDS-UPDRS improvement in both motor and non-motor symptoms 6 months after onset of stimulation[20] • Part I: improved by 3.1 points • Part II: improved by 5.3 point • Part III: improved by 13.1 points • Part IV: improved by 7.1 points 2. UPDRS improvement in score from "preoperative "off" medication to the one-year follow-up of the "off" medication "on" stimulation score"[31] UPDRS: • I: Improvement was not statistically significant • II scores improved by 73.8%. • III: significant improvement seen tremor, rigidity, bradykinesia and axial score (P<0.001 for all) • IV: dyskinesia and motor fluctuations reduced by 65.1% and 48.6%, respectively 3. UPDRS improvement in score from "the preoperative "on" medication motor subscore to the one-year follow-up "on" medication "on" stimulation score"[31] UPDRS III: significant improvement seen tremor (P=0.002), rigidity (P<0.001), bradykinesia (P=0.002), and axial score (P=0.046) 4. Baseline UPDRS motor off-medication scores improve by 30–67%[27,39,70] 5. ADLs improve by 6–56%[40,71]
Internal globus pallidus (GPi)	Strong antidyskinesia effect; Suppress cardinal PD symptoms like bradykinesia, rigidity and tremor[25]	1. Baseline UPDRS motor off-medication scores improve by 27–54%[70,72,73] 2. ADLs improve by 30–39%[40,72,73]
Newer targets		
Ventrolateral thalamus: Reduces tremor severity; relatively ineffective in improving bradykinesia and rigidity[9]		
Ventral intermediate nucleus (Vim)	Mostly effective in controlling ET[74,75] or in patients with PD and ET[26,76]	1. According to a network-meta-analysis, Vim DBS shows better improvement in UPDRS scores than GPi DBS and STN DBS in off medication phase and therefore can be used in tremor dominant PD[26] 2. The beneficial effect of Vim DBS has been seen even 10 years post procedure[77]
Pedunculopontine nucleus (PPN) Typically low stimulation frequencies are employed (20-80 Hertz) and closed-loop DBS strategies are employed.[9,78]	Effective in PD patients with predominant postural instability and gait difficulty (PIGD) Usually used with simultaneous STN DBS as its efficacy as a lone target is debatable.[78]	1. Bilateral PPN DBS alone[79] • Total UPDRS improved by 53% • UPDRS part III (motor sub score) improved by 57% • Levodopa dose reduction by 32.5% 2. Dual PPN DBS and STN DBS[80] UPDRS III reduction in off medication phase: 56% STN plus PPN DBS vs 54% STN DBS and 33% PPN DBS 3. Dual PPN DBS and STN DBS improves spinal excitability in PD.[81]

(Continued)

Table 2 (Continued).

Target	Effect	Benefit of DBS (Conventional DBS Unless Specified)
Posterior subthalamic area (PSA)	Effective in PD tremor[82]	Two years after surgery[82] • Tremor improved by 78.3% • Rigidity by 92.7% • Akinesia by 65.7% • Gait, posture and handwriting also showed improvement
Dual STN and caudal zona incerta (cZI)	cZI associated with better motor improvement than BMT, especially tremor[46]	Improvement in mean UPDRS part III score in patients with idiopathic PD was 55 ± 9% (95% CI); improvement in subscores for rigidity, bradykinesia, tremor and axial features.[47]

Abbreviations: ADL, activities of daily living; BMT, best medical treatment; CI, confidence interval; ET, essential tremor; PD, Parkinson's disease; UPDRS, Unified Parkinson Disease Rating Scale.

various fronts such as mobility, ADLs, cognition, discomfort, stigma, and emotional well-being.[40]

The overall side effect profile of both targets is similar, but speech related adverse effects, dysphagia and gait disturbances are more common in STN DBS than GPi DBS.[42–45]

As seen in this comparative review section, both STN DBS and GPi DBS are efficacious and safe targets in PD. Both STN DBS and GPi DBS have similar benefits, but a particular benefit may be more pronounced by targeting one of them. Hence, it is difficult to conclude which is a better target for DBS. Therefore, the choice between these two targets should be carefully based on the outcome desired.

New and Emerging Targets

Since, there is no consensus on the best target for DBS in PD and because no target is able to effectively manage all the patient's symptoms and QoL over a prolonged period, newer targets and dual target stimulation is being investigated to improve PD outcomes in patients with refractory motor and non-motor symptoms.[11] Stimulation of caudal zona incerta (cZI) is associated with better motor control than best medical treatment (BMT).[46] Dual stimulation of STN and cZI has been tried with better results that targeting individual regions.[47] Also, Vim, PPN, and PSA are the newer targets found to be effective in different PD patient populations (Table 2).[11]

Efficacy of Different DBS Strategies and Technologies

Efficacy of DBS is also dependent on the strategy and technology used such as cDBS, CL-DBS/aBDS, and the electrode used as these modulate the volume of tissue activated (VTA). The VTA in cDBS, CL-DBS/aBDS correlates directly with the accuracy and efficacy of the target stimulated.[9] The electrode used for DBS should be designed such that it provides a flexible interface to facilitate the application to different targets and compensate for morphological and surgical variance.[9] VTA around an optimal electrode depends on the number of contacts required for stimulation, properties of surrounding tissue and simulation parameters (frequency, amplitude and width used).[9]

Open Loop DBS or Conventional DBS

cDBS is the most commonly used strategy in PD with a known efficacy on different targets (Table 2).[6] However, since no sensor is used for feedback control of the electrical stimulation, cDBS is associated with several problems. Programming in cDBS is intricate and time consuming, and therefore needs very skilled staff.[6] cDBS needs frequent reprogramming, which adds to the treatment cost of an already costly procedure. Further continuous stimulation is associated with shorter battery life, requiring frequent surgical procedures to change battery.[6] Hence, other DBS technologies are continuously being assessed to improve patient experience and reduce treatment cost.

Closed-Loop DBS or Adaptive DBS Strategies

CL-DBS/aDBS strategies use the same electrode for sensing and stimulating and therefore minimal surgical

instrumentation is required.[9] In these strategies only the required stimulation is provided for a certain time window. Feedback control is provided by a neurophysiological biomarker (β oscillatory activity of 12–30 Hz or pulse amplitude) guided automatic adjustment of the stimulation.[6,9] This is found to be more energy efficient (unwanted direct stimulation of nearby fiber tracts is controlled), more effective in improving motor symptoms and less likely to cause speech impairment/dysarthria than cDBS.[48,49] About half the aDBS simulations delivered in the "off medication" state show efficacy; the efficacy is still higher with stimulations delivered in "on medication" state. aDBS may also be useful for patients experiencing brittle dyskinesia on STN DBS.[49] Corticopallidal CL-DBS yields greater reduction of oscillatory neuronal discharge and better alleviation of Parkinsonian akinesia.[50]

The efficacy of aDBS is, however, affected by external environmental conditions that interfere with the detection of the biomarker. These include temperature variations, functional disruptions in device, interactions with magnetic field or electric currents.[6] This problem can be overcome by using a device with multiple feedback signals.[51] Both cDBS and CL-DBS continues to face many challenges for successful integration into the treatment paradigm of PD (Figure 1).[6] Additionally these are bulkier devices than cDBS. Various micro-chip technologies are being used to constantly improve the efficacy and size of CL-DBS, but are mostly in the experimental stage.[52]

Efficacy of Different Frequency DBS

Traditionally high frequency DBS is used for electrical stimulation of the targets. However, high frequency DBS can have some adverse effects. High frequency DBS
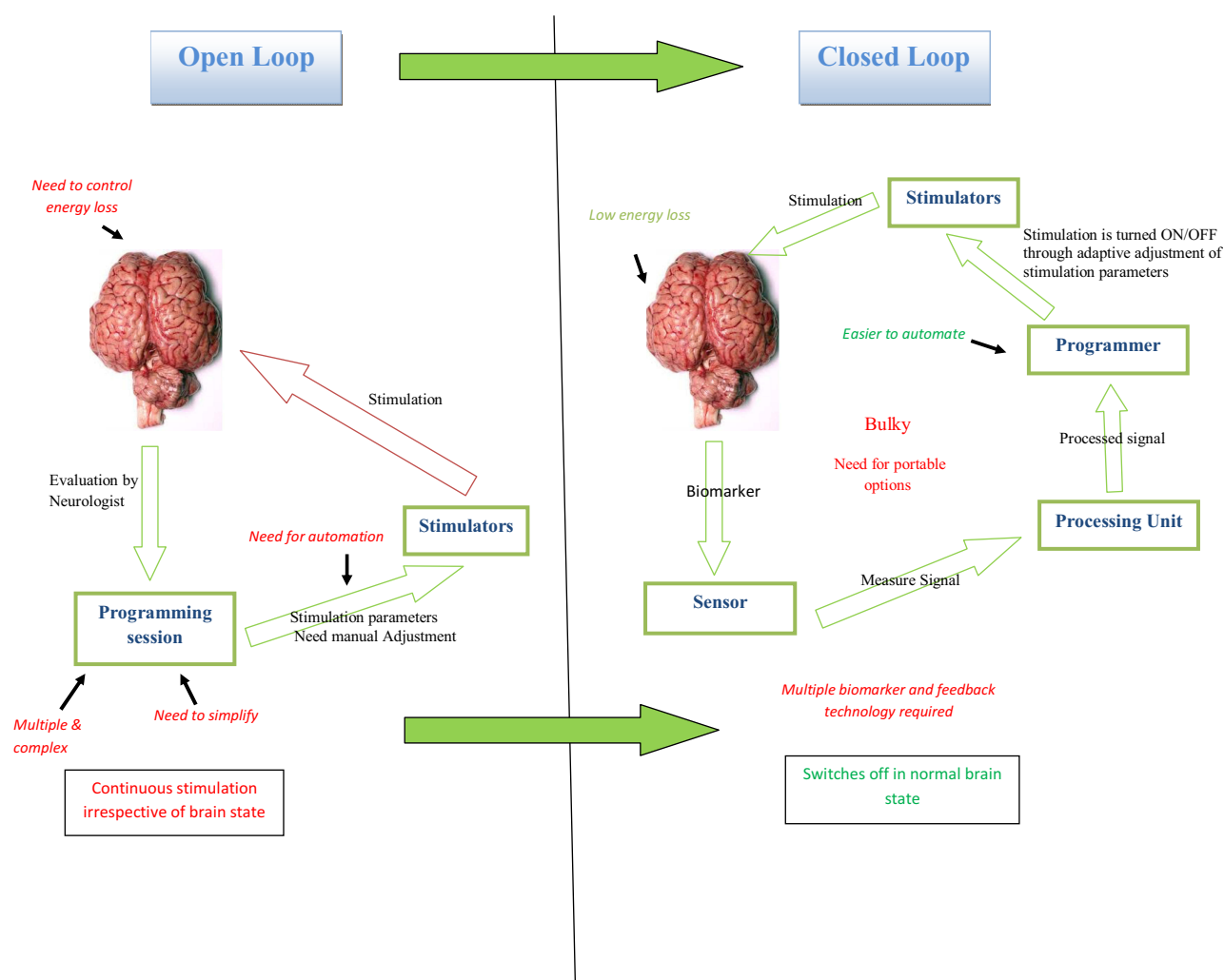
Figure 1 Open versus closed-loop DBS.

administered during a patient's decision making process can impair patient behavior.[53,54] A study showed that an adverse effect on patient's gait could be improved by alternating the simulation patterns between hemispheres based on the patient's walking pattern.[55] High frequency simulation can affect a patient's sleep quality, either positively or negatively, depending upon the DBS target used.[55,56] Therefore other frequency DBS are also being assessed for optimal stimulation patterns based on sleep, walking, gait and decision making.[57–59] However, results have been controversial and do not show a conclusive benefit of other frequencies (including low frequency) over high frequency DBS.[57–59]

DBS optimized according to the anatomy and physiology of the brain target is likely to be more effective than high frequency DBS in the long run as it will limit the amount of energy delivered, reduce side effects and induce long plastic changes.[9]

Efficacy of Segmented versus Conventional Electrodes

VTA can be modified according to requirement by using segmented electrodes instead of cylindrical ones, as this allows field steering and independent control over electrode contacts.[9,60,61] The segmented electrodes have a better design, lesser side effects, and cause lesser activation of surrounding tissue than cylindrical ones; hence they provide a larger therapeutic window and give the time to clinicians to modify side-effect thresholds.[9,60,61]

Efficacy of Local (Awake) versus General Anesthesia (Sleep) Techniques

A meta-analysis of 145 studies (n = 2563) of DBS in PD (16 on general anesthesia, GA/sleep; rest local anesthesia, LA/awake) showed that the mean target error was not significantly different between LA and GA; however the mean number of DBS lead passes were significantly less with GA as compared to LA (P = 0.006).[62] Post DBS complications (especially infections and intracerebral hemorrhage) were significantly lower with GA (P < 0.001). The two techniques did not differ significantly in UPDRS II scores "off medication", UPDRS III scores "off" and "on medication" or LED. UPDRS IV "off medication" score decreased more significantly in awake DBS versus sleep DBS cohorts (78.4% vs 59.7%, P = 0.022).[62] Hence, most DBS procedures should ideally be carried out under LA due to the lower side effect profile.

Effectiveness of DBS in Advanced versus Early PD

The efficacy of DBS in advanced PD is widely reported and assessed using MDS-UPDRS I–IV. Stimulation of different targets provides different improvements in symptoms; however, most improve motor symptoms and activities of daily living (ADL) in advanced PD. A meta-analysis of 13 randomized controlled trials found significant improvement in PD symptoms after DBS. However, GPi DBS and STN DBS resulted in similar improvement in motor scores or ADL at 36 months. STN DBS significantly reduced medication use as compared to GPi DBS (P = 0.002). GPi DBS, on the other hand, significantly improved Beck Depression Inventory scores as compared to STN DBS (P = 0.001).

However, recently efficacy of DBS in early PD is showing promising results. A meta-analysis of eight RCTs (n = 1189), of which two recruited early PD patients showed that the UPDRS, Parkinson's disease questionnaire (PDQ)-39, and LED scores improved significantly with DBS as compared to BMT (P < 0.00001).[4] Patients with early PD had a significantly greater reduction of LED than those with advanced PD (P < 0.00001). No other differences were found in efficacy outcomes between early and advanced PD.[4]

A very recent prospective randomized trial in early PD patients followed for 5-years showed that STN DBS given along with ODT significantly reduced LED (P = 0.04), polypharmacy (P = 0.01) and disease progression (especially rest tremor) (P < 0.001) compared to only on ODT.[63] Patients on DBS + ODT had a safety profile similar to patients on only ODT.

However, despite its various benefits, currently, conventionally DBS is not used in early PD.

Minimizing DBS Side Effects for Improved Efficacy

Efficacy of DBS will be higher if the safety profile is manageable and the procedure is acceptable to the patients. Since it is a surgical procedure, usual surgery associated complications such as hemorrhage, infection, and skin erosion are seen.[64] Other than these, hardware-related complications such as electrode fracture and stimulator failure have been reported.[65]

However, the most annoying, common (seen in up to 50% patients) and important postoperative complication of DBS is the side effects caused by electrical stimulation of

the surrounding brain tissue; these are largely driven by the DBS target and anatomy and functionality of the surrounding brain tissue.[66] However, these side effects are easily manageable in most cases.[66] Emerging technologies such as segmented electrodes and CL-DBS aim to minimize these side effects.[9]

Strengths and Limitations

Like most narrative reviews, this review also has a publication selection bias. DBS has evolved more slowly than medical therapy and therefore literature covered in this review could not be distributed equally over the time period covered.

However, the review has tried to assess factors driving the efficacy of DBS by covering the different parameters involved in the selection of DBS as a treatment strategy such as patient characteristics, target characteristics, pros and cons of different DBS strategies, safety of DBS and stage of PD. If clinicians can effectively use all these parameters to improve the outcomes of DBS, it will help in the better integration of this effective non-pharmacology based therapy into the treatment paradigm of PD.

Summary and Future Prospects

The review shows that DBS is an effective and evolving treatment strategy in PD. However, despite its benefits, it is not widely accepted or widely available due to cost and need for highly skilled staff to manage the programming and stimulation. Additionally, there are challenges of repeat surgeries and short battery life. DBS efficacy, accuracy and acceptability can be improved by overcoming these challenges.

Therefore, upcoming DBS technologies would need to focus on reducing electrode contact size and stimulation number, and move from an invasive to a non-invasive approach.[9,67] Newer technologies like current steering can reduce the VTA.[67] The VANTAGE study shows that multiple-source axially asymmetric directional DBS using segmented electrodes can be more efficacious than cDBS technologies without steering.[60,61] Newer biomarkers and electrode designs like rhythmic neural activity and evoked potentials for segmented electrodes can reduce the programming time.[9] Automated support tools to determine the optimal stimulation parameters can increase the penetration of technology in areas where highly skilled staff are not available.[9]

Today updated software using imaging technologies allows patient specific reconstruction of DBS leads with

fully automated tools such as PaCER.[67] Recently, a smartphone based wearable and wireless accelerometer and gyroscope platform was successfully used for quantified feedback for optimal configuration of CL-DBS tuning parameters.[68]

As highlighted in the review, DBS holds a promising place in early PD as well. Further research is required to understand patient and target selection for optimal DBS response in early PD. As newer technologies are being tried, it may be possible in the near future to move towards an automated DBS procedure that is less expensive and equally or more efficacious in both early and advanced PD.

Ethics Compliance

Not required. It's a narrative review.

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