ECRONICON OPEN ACCESS

EC NEUROLOGY
Review Article

Deep Brain Stimulation - Breakthrough in Parkinson's Disease Treatment

Srijamya[1]*, Prashant Upadhyay[2], Muhammad Wasil Khan[3], Jay Verma[4] and Aayush[2]

[1]*Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia*

[2]*Government Medical College, Jalaun, Uttar Pradesh, India*

[3]*Ziauddin Medical College, Pakistan*

[4]*Maulana Azad Medical College, India*

***Corresponding Author:** Srijamya, Faculty of Medicine, Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia.

Received: October 04, 2021; **Published:** October 28, 2021

Abstract

Importance: Deep Brain Stimulation [DBS] has been a breakthrough advancement in recent years in the treatment of Parkinson's disease. The altercation still goes on the effectiveness of the unilateral and bilateral DBS but the patients in different stages of Parkinson's disease have shown effective results with both unilateral and bilateral DBS.

Observations: Research and trials have shown the many beneficial outcomes of DBS in Parkinson's disease. These are pruning of motor fluctuation severity, a reduced daily dose of levodopa, and enhancement of sleep quality and cognitive functions. There are some disadvantages of DBS with the surgical procedure, implants, and their stimulation. These disadvantages can be conquered by advancements in the technology of DBS. The evolution in the DBS implants like connectivity of electrodes with automatic sensing technology, long battery life and connectivity with wifi can facilitate better outcomes of DBS in progressive neurodegenerative Parkinson's disease.

Conclusion: Motor symptoms of Parkinson's disease and sleep quality have been seen to be improved with DBS. Negative symptoms like anhedonia, social withdrawal, etc. which are seen in patients with Parkinson's disease do not show any reduction or improvement with DBS.

Keywords: *Parkinson's Disease (PD); Deep Brain Stimulation*

Abbreviations

PD: Parkinson's Disease; DBS: Deep Brain Stimulus; STN: Subthalamic Nucleus; IPG: Implantable Pulse Generator; Gpi: Globus Pallidus Internus; V: Volt; Ma: Milli Ampere; NICE: National Institute for Clinical Excellence; ADL: Activities of Daily Living; FDA: Food and Drug Administration; UPDRS: Unified Parkinson's Disease Rating Scale; CAPIT: Core Assessment Program for Intracerebral Transplantations; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; BCBSA: Blue Cross and Blue Shield Association; MAP: Medical Advisory Panel; TEC: Technology Evaluation Centre; VIN: Ventral Intermediate Nucleus

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders affecting mainly the geriatric population, having an estimated worldwide disease burden of nearly 5 million. It is clinically characterized by four main symptoms: resting tremor, ataxia, rigid-

ity and bradykinesia [1]. The current management of PD is multifaceted, including pharmacological treatment, surgical interventions, and supportive (exercise, canes, walkers etc.) care. A combination of these treatment options is tailored to the needs of each patient, and there is no single universally accepted approach.

Surgical management of PD involves a procedure known as Deep Brain Stimulation (DBS) in which a neurostimulator is placed under the chest wall; it then sends electrical impulses to electrodes implanted in specific brain regions [2]. There have been significant technological advancements and expansions in DBS applications since its introduction in the 1980s. In Parkinson's Disease, the main objective of employing DBS is to improve and control motor symptoms. Typically, it has been used in patients with intermediate to late motor complications, but given the clinical heterogeneity of cases, many considerations need to be made when choosing the candidates.

The precise mechanisms through which DBS operates have remained elusive and researchers have put forward a number of hypotheses from time to time. It appears that a multitude of therapeutic mechanisms are at play, such as disruption of information flow, neuroprotection as well as modulation of glia mediated transmission, electrotaxis and cortical plasticity [3,4]. However, a unified model elucidating the function of DBS still does not exist.

Here we have reviewed the current evidence on the efficacy of DBS in improving PD motor symptoms as well as present a detailed account of patient indications for unilateral and bilateral DBS in order to provide directions for its use in clinical practice and a stepping stone for future research in this area.

History

DBS was first developed in 1987 by a group of professionals in Grenoble, France, who were treating patients with essential tremor and Parkinson's disease (PD). Despite the fact that many professionals have known about neurostimulation's therapeutic benefits for decades and that neurostimulation technology had been in development since the 1960s, Stereotactic surgery was utilized to treat a range of mental disorders (including psychosurgery), chronic pain, and mobility restrictions during this period of significant development.

The developing concept of stereotactic apparatus, which delineates the brain as a three-dimensional (3D) system of Cartesian coordinates and is assisted by imaging technology, resulted in a breakthrough in December 1997, when the Blue Cross and Blue Shield Association (BCBSA) Medical Advisory Panel (MAP) discovered that unilateral DBS of the thalamus for patients with medically unresponsive tremor due to Parkinson's disease met the Technology Evaluation Center (TEC) criteria for patient safety.

In 2002, the US Food and Drug Administration (FDA) authorized DBS for the treatment of Parkinson's disease, providing Medtronic clearance for the treatment with medicines. DBS has now been used to treat approximately 40,000 people with Parkinson's disease and essential tremor all around the world, with a pacemaker-like device delivering constant electrical stimulation to brain regions [6].

The Infinitely DBS directional 4 contact lead system received ET and PD approval in 2016. Boston Scientific stated in 2017 that the Vercise DBS system for PD had been approved, including several independent power sources for an additional 8 completed connections on the DBS [7].

Working mechanism of DBS in Parkinson's disease

DBS's mechanism of action is unconfirmed. High frequency stimulation was originally thought to have an inhibiting impact. However, a recent hypothesis by Chiken and Nambu [39] suggests that DBS may disrupt information flow through a specific region in order to mimic the effects of an undefined permanent lesion. DBS is also thought to act via a number of nonexclusive mechanisms, such as local and network-wide electrical and neurochemical responses of stimulation, oscillatory processes modification, plasticity of synapses, and,

presumably, neuroprotection and neurogenesis. Considering the vastness of proposed mechanisms, the details of each are not discussed as it is beyond the scope of this article [7,8].

For now, though, three potential sites for DBS treatment of Parkinson's disease have been identified: the ventral intermediate nucleus of the thalamus (Vim), the globus pallidus pars interna (GPi), and the subthalamic nucleus (STN). Only the device for unilateral chronic DBS of the ventral intermediate nucleus (Vin) of the thalamus has been approved by the FDA for the management of patients with tremor-dominant Parkinson's disease or other tremor related disorders since it is linked to a higher incidence of speech, swallowing, and cognitive disabilities. Also, bilateral DBS of the Vim is rarely performed [9].

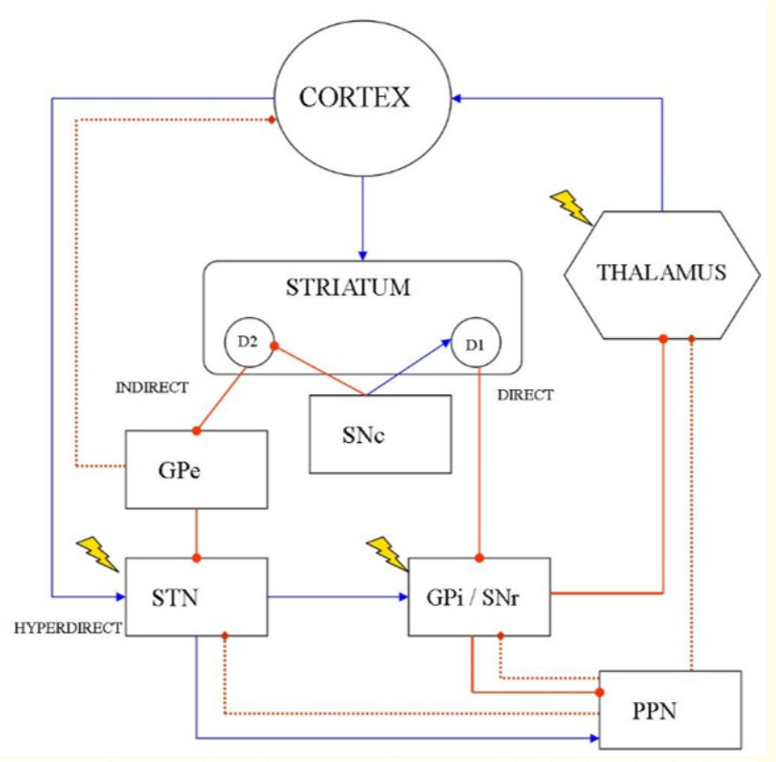

FIGURE: Mechanism of Deep Brain Stimulation in Parkinson's Disease representation through Cortico-basal-ganglia-thalamo-cortical circuitry. The direct, indirect, and hyperdirect pathways are indicated. Red lines denote inhibitory connections, blue lines denote excitatory connections, and brown dotted lines denote mixed cholinergic, GABAergic, and glutamatergic connections. Of note, the pedunculopontine nucleus (PPN) also exhibits anatomic projections to striatum and cortex (omitted for clarity). DBS stimulates the local neurons at the targeted site, thereby further activating the inhibitory neurons which decreases the firing of the surrounding neurons by intrinsic firing in cell bodies resulting in overall decreased voltage gated currents. Cortical stimulation induces a triphasic response composed of early stimulation, inhibition and late excitation. The balance between the inhibition and excitation of action potentials at various different levels of brain results in decreased motor symptoms as seen in PD.

KEY: Mixed
Inhibitory
Excitatory
Target Sites for DBS

D: Dopamine Receptor
GPe: Externus Globus Pallidus
SNc: Substantia Nigra Pars Compacta
STN: Subthalamic Nucleus
GPi/SNr: Internus Globus Pallidus/ Substantia Nigra Pars Reticulata
PPN: Pedunculopontine Nucleus

Figure 1

DBS technology

The Activa® (FDA licensed in 1997) and Percept® (FDA approved in 2020) systems manufactured by Medtronic, Inc. are currently employed in routine clinical practice for DBS. There are other devices available too with similar mode of action, Infinity by Abbott (FDA approved 2016) and Vercise by Boston Scientific (FDA approved 2017). The quadripolar electrode (four contact sites arranged along the distal edge) is stereotactically implanted into the targeted nucleus (STN or GPi) in a bilateral procedure similar to the corresponding ablative procedure. To increase symptom relief, changes can be made to the electrode contact site, stimulation pulse amplitude, frequency and width [7].

Components of the commercially available implantable deep brain stimulation system includes:

1. **Implantable components:** DBS™ Lead (a thin, insulated cable with four electrodes at the tip, inserted within the brain); Neurostimulator (a compact, sealed device implanted beneath the skin in the chest); Extension of the lead (a thin, insulated wire implanted under the skin of the head and neck, connecting the lead to the neurostimulator).

2. **Components for system "start-up"/programming stimulation parameters:** Physician Programmer with Memory Mod software cartridge and Neurological Testing Stimulator (used to test the effectiveness of the system prior to implantation) (to allow the system to be noninvasively adjusted).

3. **Patient components:** Hand held control magnet (for turning the system on and off) When implantation is performed bilaterally, two separate DBS systems must be used according to U.S. Food and Drug Administration [10].

Patient indications

Patients with idiopathic Parkinson's disease, whose symptoms are responsive to levodopa, and patients whose disease is complicated by motor complications that cannot be managed with medications (complications such as "on-off" fluctuations with periods of severe immobility, presence of 'off' period dystonic posture, or refractory levodopa-induced dyskinesia) may benefit from unilateral and bilateral DBS of STN-subthalamic nucleus or GPi-Globus Pallidus Internus.

Contraindications

Absolute contraindications: Significant cognitive dysfunction, structural abnormalities in magnetic resonance images, dementia and active psychiatric symptoms.

Relative contraindications: Surgical risk, severe non-motor symptoms, severe dysarthria, unrealistic patient expectations, lack of family support and poor motivation.

Target selection and identification

Currently, the two main DBS targets being investigation are relatively small structures. The STN is a tiny, oval nucleus in humans, with a volume of 150 - 200 cubic mm. It is 2 - 3 mm superior and somewhat lateral to the substantia nigra, 1 - 2 mm anterior to the red nucleus, and posterior to the mamillary bodies, with the internal capsule circumscribed exteriorly.

The GPi is a small structure in the brain with a volume of about 500 cubic mm. It is bounded dorsolaterally by the globus pallidus externa, caudally by the internal capsule, and ventrally by the optic tract. Sensorimotor areas with somatotopic organization are seen in both structures, indicating their anatomical complexity.

As target identification methods differ, there is dispute on whether a target may be identified purely by anatomic (imaging) means or through a combination of anatomic and physiologic (micro-recording and micro-stimulation) approaches. Image technology has been demonstrated to have a 75 percent inaccuracy rate in targeting. However, no data exists that precisely indicates how precise the electrode site of action must be in order to produce the optimum therapeutic results [11].

Imaging with MRI, ventriculography, macroelectrode stimulation (allows delineation of the boundaries of the targeted nucleus and surrounding structures), or micro-stimulation and micro-recording are all employed to determine the location of the ideal target site (permits definition of the somatotopic organisation of the targeted nucleus).

More recent research suggests that bilateral DBS of the GPi or STN may relieve the whole constellation of parkinsonian symptoms in people with early PD (tremor, rigidity, and bradykinesia). As a result, research has switched to these areas, which appear to be more appropriate targets for DBS in advanced stages of Parkinson's disease than the thalamus. DBS of the STN or GPi, unless contraindicated, requires a bilateral surgery to attain better therapeutic outcomes in individuals with pre-existing parkinsonian symptoms [12].

Surgical implantation procedure

There are established prerequisites for patients to be eligible for DBS and further follow up visits confirms whether the patient is the right candidate for receiving the DBS unilateral and bilateral approach.

The four essential components that make up the DBS procedure are about as follows: A period of stereotactic image acquisition and coordinated calculation, aided by computed tomography (CT) or magnetic resonance imaging (MRI), followed by a stereotactic neurosurgical procedure consisting of drilling a burr hole in the cranium and passing a probe through brain tissue to the target, all while under local anaesthetic, followed by implantation of the DBS electrode with interoperative stimulation. The insertion of a pulse generator is followed by a general surgical operation under general anaesthetic, and finally the setting and programming of stimulation parameters.

The DBS electrode is placed, further stabilized, and then linked to a transcutaneous cable for short-term stimulation for initial assessment once the target site is finalized using a micro- or macro-electrode probe. The length (7.5 mm and 10.5 mm) and distance between active sites of the two DBS electrode types now in use differ (0.5 mm and 1.5 mm respectively). They are both tetrapolar and have a diameter of 1.27 mm. The electrode is attached to the cranium (skull) and connected to its percutaneous extension after the exact placement is confirmed by control imaging examinations. Following electrode implantation, the patients are admitted to the hospital for a week to assess and monitor their responses, which includes follow-up MRI studies, adjustment and evaluation of stimulation parameters, surgical implantation of programmable stimulators, and subcutaneous connection of stimulator and electrode extension. In addition, hospitalization is recommended to ensure prompt hospital care in the case of a medical emergency [8,13,14].

Unilateral vs bilateral DBS

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus internus (GPi) is now considered a safe and effective surgical treatment for Parkinson's disease (PD) based on randomised controlled trials with motor symptom scales as primary and Quality of Life (QoL) as secondary outcomes. A set of standardised tests are used to assess clinical outcomes in the treatment of Parkinson's disease. The Unified Parkinson's Disease Rating Scale (UPDRS) is the most commonly used, but other tests such as the Schwab and England scale, various timed tests, scales developed for the Core Assessment Program for Intracerebral Transplantations (CAPIT), tests that quantify tremor and dyskinesia, and questionnaires for patient and caretaker approval evaluation are also available for further confirmation.

Considering the comparison as to choose either unilateral or bilateral DBS is effective, there are different views about this. There are several researches which give detailed comparisons of the both of these treatment methods. The variation in case presentation of each patient is likely key factor in determining which method is supposed to be prescribed. Following is the basic comparisons from a research about the above-mentioned treatment modalities.

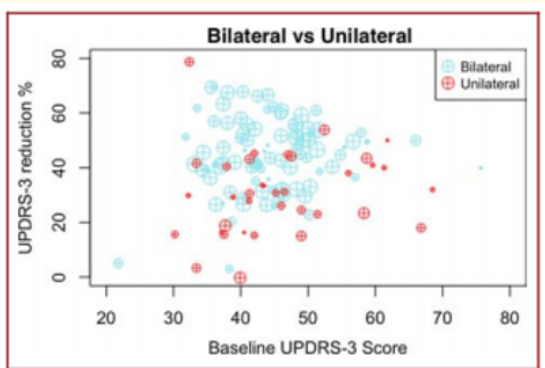

FIGURE 5. *Scatterplot demonstrating UPDRS-3 reduction for bilateral vs unilateral, over baseline UPDRS-3 scores. Bilateral treatment provided greater efficacy than unilateral treatment. There was no association between baseline score and efficacy outcome or baseline score and bilateral vs unilateral. Size of data point represents number of patients in the study.*

Figure 2: *(Adapted from DOI:10.1093/neuros/nyaa485).*

Efficacy of DBS in Parkinson's disease

The UPDRS is the most extensively used metric for evaluating Parkinson's disease treatment. It contains a comprehensive list of Parkinson's disease signs and symptoms, organized into sections on activities of daily living and motor function, mood, mentation, muscle rigidity, speech and gait.

The total inventory score ranges from 0 to 176, with 0 being the best and 176 being the worst. The patient is regarded to be "off medication" if testing is done before the first early morning dosage of levodopa and at least 12 hours after the previous day's last dose of levodopa. As levodopa becomes less effective and motor fluctuations grow more frequent and severe, this strategy is meant to mimic the degree of symptoms patients experience in their daily lives. According to usual protocol, the "on medication" state is defined as the patient's best test scores recorded during the day when taking levodopa. In other trials, "on" scores are recorded during a "best 'on' state" generated by a suprathreshold levodopa dosage [8,15,16].

An assessment tool that is solely used to monitor performance in daily activities can be obtained by Schwab and England scale which is measured in "off" and "on" states. The scoring is reversed from the UPDRS: a score of 100 indicates normal, while a score of 0 shows total disability [8,17].

While there have been reports of benefits such as reduced motor fluctuations, dyskinesias, and significant improvements in the motor and activities of daily living (ADL) scores on the Unified Parkinson's Disease Rating Scale (UPDRS) in the "off" state, no studies have shown any reduction in daily levodopa dose. However, DBS of the GPi has been associated to inducing dyskinesia with the first electrode and blocking the levodopa response with the ventral electrode in some situations. These issues, together with preliminary evidence that the STN may be a better target site, have prompted many centers to refocus their research efforts on bilateral DBS of the STN as the new treatment technique [18].

DBS was approved by NICE (National Institute for Clinical Excellence) and FDA (Food and Drug Administration) for treatment of late stages of parkinsonism in year 2002 [19]. It was found more beneficial than the possible existing medical therapy available till date that is Levodopa with or without Carbidopa in improving the chief symptoms tremors, bradykinesia and rigidity [19-21]. Though the overall best DBS target site for parkinsonism patient remains debatable, STN and GPi are two DBS sites which are most extensively studied and found to be more effective.

STN and GPi DBS are found similar in terms of efficacy in ameliorating the characteristic devastating features like tremors, bradykinesia and rigidity especially in the "on" phase [22-25]. In the "off" phase, however, STN DBS has been found to be more effective than GPi DBS [22,25-27]. Multiple studies on STN DBS have shown significant rectification of motor symptoms especially tremors as due to small size of STN, complete stimulation of the region is achieved, progressively improving the motor symptoms for up to 5 years of follow up after DBS surgery [28,29]. It also improves the quality of sleep-in patients as evaluated on PDSS (Parkinson Disease Sleeping Scale), while GPi DBS have no significant effect on the sleep quality [28].

Adequate combination of various stimulation parameters like intensity, frequency, pulse width and directional stimulation are very important to increase the effectiveness of DBS procedure. Rizzone., *et al*. in their study on STN DBS showed that 0.7 mA to 1.7 mA stimulation intensity produces loss of wrist rigidity, while adverse effects were observed at and above 3.4 mA [30]. Bradykinesia, rigidity and tremors shows positive therapeutic response with STN DBS used at 2V and 3V voltage settings and no additive benefits were found above 3V [31]. Regarding frequency in STN DBS, it was observed that all frequencies over 50 Hz significantly improves bradykinesia and tremors and 33 Hz was the threshold for positive outcome in rigidity symptoms. Frequencies below 50 Hz were not associated with any improve-

ment in outcome rather causing further worsening of tremors [31]. Keeping the pulse width at 60 μs and 210 μs showed significant reduction in bradykinesia, also there exists an inversely proportional relationship between pulse width and the therapeutic index of the DBS procedure [32].

The long-term outcomes of DBS also depend largely on screening and adequate patient selection, screening the functioning of hardware and battery in implantable pulse generator (IPG), correct placement of DBS leads, adequate parameter programming and correct localization of co-ordinates of DBS target sites [33].

Large size of GPi (around three times of STN), requires high amplitude, pulse width and high frequency for stimulation resulting in frequent battery changes as compared to STN DBS which in turn further increases the risk of surgical complications and spreading of infections during re-implantation of the battery subcutaneously in the subclavicular space [23,34]. Also, STN being smaller in dimensions may lead to dispersion of stimulation pulse to adjacent limbic or associated regions causing cognitive and psychiatric side effects which is seen less frequently with GPi DBS [35], while some studies showed absence of any significant difference in cognitive and psychiatric benefits between STN and GPi DBS at 3 years of follow up [35]. Parkinson's disease being a progressive neurodegenerative disorder which puts a potential limitation to DBS treatments option as DBS does not prevent this neurodegeneration due to which the disease keeps progressing with time, which is one of the biggest limitations of DBS along with the high-cost burden of DBS procedure [36].

Discussion

DBS has made established advancements in the medicament of movement disabilities and neuropsychiatric disorders including Parkinson Disease, Essential tremor and dystonia.

Focusing on DBS in the regimen of Parkinson's disease treatment, there are bulk of research and patient work done and the results are in favour of patients. Patients have shown a positive response with unilateral DBS in late stages of the disease and the most effective location that showed most positive response was subthalamic nucleus (STN). Key beneficial health outcomes include:

- Reduction in severity of motor fluctuations and in the amount of time spent in the "off" state each day;
- Improvement in parkinsonian motor disability in the 'off' condition as measured by UPDRS motor and ADL scores;
- Refinement of motor disability during 'on' periods and trimming in severity of levodopa induced dyskinesias;
- Reduction in the required daily dose of levodopa or its equivalents.

Other possible beneficial health outcomes include improvement in specific cardinal symptoms of Parkinson's disease (tremor, rigidity, bradykinesia, gait disturbance), in sleep quality, appetite, cognitive function and mood. The bilateral DBS is found to be beneficial in early stage of the disease.

Although in the medical practice, personalized medication is kept in focus and hence patient profile must be analyzed thoroughly for making DBS process more effective by modulating the process according to the patient's symptoms. Adverse outcomes are those conditions associated with the:

- Surgical procedure (hemorrhage, ischemic lesions, seizures, adverse cognitive effects, complications of general anesthesia); surgical target error rate is as high as 75%.
- Device (displacement or migration of the electrode, skin erosion or infection, mechanical problems with the electrical system such as battery failure and fracture of implanted materials);

- Stimulation (effects such as paresthesia, muscle contraction, pain, abnormal eye movement, adverse cognitive effects, psychological affects like anger) [13,37].

The side effects must also be monitored through regular follow up. Considering the advancement in the DBS devices through modern technology, it can be acknowledged that in the upcoming decade these devices will continue to shape the future selection of various different neurological stimulators [38]. DBS system still has a lot of area for the development and progress which would be proved beneficial for the patient. The improvement in the technology of DBS system would help in increasing effectiveness and reducing device related problems reducing multiple surgeries. Implantable pulse generator size reduction and fixed position would lead to reduced chance of electrode displacement. Longer battery life and connection of the device to the mobile system and electrodes automatic sensing and stimulating would increase the effectiveness of DBS system in future [39].

Conclusion

Parkinson's disease treatment is determined according to the disease stage and the patient's response to the treatment. The motor symptoms are seen improving with deep brain stimulus. The sleep quality is also seen to be improved in the patients after using deep brain stimulus. The stimulus pattern and the frequency of stimulation of the (DBS) deep brain stimulus is the key factor to be determined according to the particular patient profile. Negative symptoms [anhedonia, flat affect, avolition, social withdrawal, reduction in normal functioning and encompass apathy and psychomotor retardation] of Parkinson's disease have not been seen to be improved with the deep brain stimulus. Moreover, Parkinson's disease is a progressive neurodegenerative disorder and the approved conventional treatment options for it remains to be limited with no effect on the disease progression and merely providing only symptomatic relief. extensive research and study work is being carried out going on in the field for refinement of the existing treatment options and to find other potentially effective treatment modalities such as DBS, gene therapy, etc aimed at reducing and preventing the progression of Parkinson's disease.

Ethical Approval and Consent to Participate

Approved.

Consent for Publication

As a corresponding author, I, Srijamya, giving consent for publication.

Availability of Supporting Data

Competing Interests

Not applicable.

Funding Support

Not applicable.

Authors' Contributions

Jay Verma and Muhammad Wasil Khan worked hard to collect all the important and verified research papers on the topic. Dr. Prashant Upadhyay made outline of the review paper and concluded all his studies under the efficacy of DBS as a treatment. Dr Prashant and Dr Aayush helped in reviewing and editing work. Srijamya compiled the whole review under abstract, discussion and conclusion.

Acknowledgements

I, Srijamya, corresponding author, am really grateful to my professor of neurology who guided me to find my interest in neurology and research work. My parents and colleagues support must be underlined and highlighted as they are the pillars of all the achievements of my life.

Bibliography

1. Olanow C Warren., *et al.* "Parkinson's Disease and Other Movement Disorders". Harrison's Principles of Internal Medicine, edited by Dennis L. Kasper, Stephen L. Hauser, J. Larry Jameson, Anthony S. Fauci, Dan L. Longo, Joseph Loscalzo, McGraw Hill Education (2015): 2609.

2. Krauss JK., *et al.* "Technology of deep brain stimulation: current status and future directions". *Nature Reviews Neurology* 17.2 (2021): 75-87.

3. Stefani A., *et al.* "Mechanisms of action underlying the efficacy of deep brain stimulation of the subthalamic nucleus in Parkinson's disease: central role of disease severity". *European Journal of Neuroscience* 49.6 (2019): 805-816.

4. Ashkan K., *et al.* "Insights into the mechanisms of deep brain stimulation". *Nature Reviews Neurology* 13.9 (2017): 548-554.

5. Gardner J. "A history of deep brain stimulation: Technological innovation and the role of clinical assessment tools". *Social Studies of Science* 43.5 (2013): 707-728.

6. Lozano AM., *et al.* "Deep brain stimulation: current challenges and future directions". *Nature Reviews Neurology* 15.3 (2019): 148-160.

7. Alegret M., *et al.* "Effects of bilateral subthalamic stimulation on cognitive function in Parkinson disease". *Archives of Neurology* 58.8 (2001): 1223-1227.

8. Tisch S., *et al.* "Pallidal stimulation modifies after-effects of paired associative stimulation on motor cortex excitability in primary generalised dystonia". *Experimental Neurology* 206.1 (2007): 80-85.

9. Benabid AL., *et al.* "Deep brain stimulation of the subthalamic nucleus for Parkinson's disease: methodologic aspects and clinical criteria". *Neurology* 55.12-6 (2000): S40-44.

10. Deep-Brain Stimulation for Parkinson's Disease Study Group Obeso JA., *et al.* "Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease". *The New England Journal of Medicine* 345.13 (2001): 956-963.

11. Jahanshahi M., *et al.* "The impact of deep brain stimulation on executive function in Parkinson's disease". *Brain* 123.6 (2000): 1142-1154.

12. Ashby P and Rothwell JC. "Neurophysiologic aspects of deep brain stimulation". *Neurology* 55.12-6 (2000): S17-20.

13. Brooks DJ and Samuel M. "The effects of surgical treatment of Parkinson's disease on brain function: PET findings". *Neurology* 55.12-6 (2000): S52-59.

14. Deep-Brain Stimulation for Parkinson's Disease Study Group Obeso JA., *et al.* "Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease". *The New England Journal of Medicine* 345.13 (2001): 956-963.

15. Odekerken VJ., *et al.* "Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial". *The Lancet Neurology* 12.1 (2013): 37-44.

16. Taba HA., *et al.* "A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort". *Journal of Neurosurgery* 113.6 (2010): 1224-1229.

17. Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) or the globus pallidus interna (GPi) for treatment of advanced Parkinson's disease". *Tecnologica MAP* (2001): 1-8.

18. Okun MS. "Tips for Choosing a Deep Brain Stimulation Device". *JAMA Neurology* 76.7 (2019): 749-750.

19. Bratsos S., *et al.* "Efficacy and Safety of Deep Brain Stimulation in the Treatment of Parkinson's Disease: A Systematic Review and Meta-analysis of Randomized Controlled Trials". *Cureus* 10.10 (2018): e3474.

20. Perestelo-Pérez L., *et al.* "Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials". *Journal of Neurology* 261.11 (2014): 2051-2060.

21. Thevathasan W., *et al.* "Movement Disorders Society PPN DBS Working Group in collaboration with the World Society for Stereotactic and Functional Neurosurgery. Pedunculopontine nucleus deep brain stimulation in Parkinson's disease: A clinical review". *Movement Disorders* 33.1 (2018): 10-20.

22. Odekerken VJ., *et al.* "Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial". *The Lancet Neurology* 12.1 (2013): 37-44.

23. Follett KA., *et al.* "CSP 468 Study Group. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease". *The New England Journal of Medicine* 362.22 (2010): 2077-2091.

24. Liu Y., *et al.* "Meta-analysis comparing deep brain stimulation of the globus pallidus and subthalamic nucleus to treat advanced Parkinson disease". *Journal of Neurosurgery* 121.3 (2014): 709-718.

25. Xu H., *et al.* "Subthalamic nucleus and globus pallidus internus stimulation for the treatment of Parkinson's disease: A systematic review". *Journal of International Medical Research* 45.5 (2017): 1602-1612.

26. Tan ZG., *et al.* "Efficacies of globus pallidus stimulation and subthalamic nucleus stimulation for advanced Parkinson's disease: a meta-analysis of randomized controlled trials". *Clinical Interventions in Aging* 11 (2016): 777-786.

27. Mao Z., *et al.* "Comparison of Efficacy of Deep Brain Stimulation of Different Targets in Parkinson's Disease: A Network Meta-Analysis". *Frontiers in Aging Neuroscience* 11 (2019): 23.

28. Okun MS and Foote KD. "Subthalamic nucleus vs globus pallidus interna deep brain stimulation, the rematch: will pallidal deep brain stimulation make a triumphant return?" *Archives of Neurology* 62.4 (2005): 533-536.

29. Liu Y., *et al.* "Subthalamic nucleus deep brain stimulation improves sleep in Parkinson's disease patients: a retrospective study and a meta-analysis". *Sleep Medicine* 74 (2020): 301-306.

30. Rizzone M., *et al.* "Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: effects of variation in stimulation parameters". *Journal of Neurology, Neurosurgery, and Psychiatry* 71.2 (2001): 215-219.

31. Dayal V., *et al.* "Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease: The Effect of Varying Stimulation Parameters". *The Journal of Parkinson's Disease* 7.2 (2017): 235-245.

32. Reich MM., *et al.* "Short pulse width widens the therapeutic window of subthalamic neurostimulation". *Annals of Clinical and Translational Neurology* 2.4 (2015): 427-432.

33. Wagle Shukla A and Okun MS. "Surgical treatment of Parkinson's disease: patients, targets, devices, and approaches". *Neurotherapeutics* 11.1 (2014): 47-59.

34. Weaver FM., *et al.* "CSP 468 Study Group. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes". *Neurology* 79.1 (2012): 55-65.

35. Boel JA., *et al.* "NSTAPS study group. Cognitive and psychiatric outcome 3 years after globus pallidus pars interna or subthalamic nucleus deep brain stimulation for Parkinson's disease". *Parkinsonism and Related Disorders* 33 (2016): 90-95.

36. Unilateral vs. "Bilateral Subthalamic Stimulation in Parkinson's Disease (P1.168) Sara Duffus, Ugonma Chukwueke, Roy Strowd, Jennifer Green, Ihtsham Haq, Jessica Tate, Maja Herco, Adrian Laxton, Stephen Tatter, Mustafa Siddiqui Neurology 84.14 (2015):168.

37. Lyons KE., *et al*. "Long term safety and efficacy of unilateral deep brain stimulation of the thalamus for parkinsonian tremor". *Journal of Neurology, Neurosurgery, and Psychiatry* 71.5 (2001): 682-684.

38. Gardner J. "A history of deep brain stimulation: Technological innovation and the role of clinical assessment tools". *Social Studies of Science* 43.5 (2013): 707-728.

39. Chiken S and Nambu A. "Mechanism of Deep Brain Stimulation: Inhibition, Excitation, or Disruption?" *Neuroscientist* 22.3 (2016): 313-322.

Volume 13 Issue 11 November 2021