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Efficacy of Deep Brain Stimulation (DBS) Across Stages of Parkinson's Disease

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Abstract

Deep brain stimulation (DBS) is a proven intervention in the treatment of Parkinson disease (PD), which offers substantial control of motor symptoms, medication-saving and quality of life to a well-selected population. This narrative review is a summary of the current evidence on the efficacy of DBS through the PD spectrum of outcomes, with an emphasis on motor and non-motor outcomes and patient response modifiers. This narrative review provides a summary of the existing research on DBS effectiveness throughout the PD spectrum, motor outcomes, non-motor outcomes, and variables affecting patient response. Early-stage DBS, used shortly after the development of motor complications, can deliver long-term motor utility, lessening the overall load of dopaminergic drugs, and cognitive safety in the selected patients. DBS has been very effective in treating treatment-resistant motor symptoms of PD in severe forms but non-dopaminergic symptoms, including gait, balance disorders, and cognitive impairments, can end up being the determinants of the final results in the disease. The choice of the target between the subthalamic nucleus (STN) and globus pallidus internus (GPi) must be made on a case-by-case basis, given the possibility of a higher medication reduction with STN-DBS compared to more desirable neuropsychiatric profile of GPi-DBS in at-risk patients. The non-motor outcomes are not stable, and it is the reason to consider the necessity to carry out a comprehensive preoperative assessment, patient education and multidisciplinary focus. Although strong evidence is offered in support of DBS, the study has limitations such as the lack of long-term quality of life and non-motor outcomes data and standardized stimulation and assessment protocols. The future research

must be devoted to large and prospective trials comparing early and delayed DBS, patient selection by neuroimaging and genetic biomarkers and by applying extensive technological breakthroughs, including adaptive and closed-loop stimulation. The optimal integration of DBS in the management of PD will be important to address the problem of underutilization, cost-effectiveness, and fair access.

Keywords: Parkinson's disease, Deep brain stimulation, Subthalamic nucleus, Motor symptoms, Disease progression.

Introduction

Parkinson's disease (PD) is a neurology disorder that gets worse over time and is mostly characterized by the death of dopamine-producing neurons in the substantia nigra which leads to the appearance of a typical set of motor symptoms tremor, bradykinesia, rigidity, and postural instability as well as a large number of non-motor disturbances including cognition, mood, autonomic balance, and sleep (1). The disorder has quickly grown in prevalence during the last several decades, mainly due to the aging of the population, increased life expectancy, and the use of more precise diagnostic methods. It is currently estimated that more than eleven million people worldwide are affected by the disorder, and the projections are such that the incidence and disability resulting from it will continue to grow till the middle of the 21st century (2). The trajectory of the disease has significant repercussions, steadily straining the healthcare systems and at the same time, making the burden on the patients and their support systems more intense both physically and psychologically as well as by their financial status.

The initial pillar of PD management is pharmacologic therapy, which is always the first option in PD management, and levodopa is still the most potent drug used in the control of early motor symptoms. However, even though the therapy started out to be very effective, the long-term treatment is usually the case that the patient goes through motor fluctuations, sudden "on-off" changes, and levodopa-induced dyskinesias; Moreover, the clinical pathways of patients treated with this drug are often made more complex due to the accumulation of non-motor adverse effects, thus requiring more than just medication adjustments to resolve them (3). The use of adjunctive drugs can postpone these occurrences, but they hardly ever eliminate them completely. As a result, many patients reach a point in their treatment where the disease progresses faster than the drug effect, thus, getting the maximum therapeutic effect. At this point, sometimes deep brain stimulation (DBS) is unveiled. Besides, continuous and targeted electrical stimulation is directed towards the subthalamic nucleus (STN) or the globus pallidus internus (GPi), thus, modulating the dysfunctional basal ganglia circuits. Tremor, rigidity, bradykinesia, dyskinesia, and motor fluctuation all get to experience substantial reductions due to this modulation (4).

Many patients indicate a substantial enhancement of motor performance that correlates with a tremendous reduction of the dosage of dopaminergic drugs, and even though the motor aspects are not as obvious as the non-motor ones, nevertheless, most domains indicate a change (5). DBS has therefore become a known option of treatment among the appropriately selected patients with medication-

refractory symptoms. Despite the fact that it has been proved to be efficient, there are still some doubts how and when to use DBS and how the effects that will result are dependent on the phase of the illness. The studies conducted on the precedent treatments, specifically the EARLYSTIM trial, show that the benefits of the DBS are sustained in the long term provided that it is implemented as soon as the motor complications have appeared (6). On the other hand, research focusing on patients who have a more severe disease, have experienced symptoms for a longer time, have changes in cognition or have difficulties in movement reveal that the outcomes and postoperative recovery are more diverse and have a wider range (7).The differences here clearly indicate that there is still a lot of uncertainty regarding the advantages, dangers, and projections of the various states of the disease over a long period of time. Therefore, this review will be the one that will pull together the present evidence on the effectiveness of DBS in the entire PD progression history. Through an assessment of clinical outcomes, complication profiles, medication adjustments, and patient selection considerations, the review will attempt to make it clear how the stage of disease impacts the therapeutic response and will also specify the implications for clinical decision-making and future research (7).

Methodology

This narrative review was aimed at summarizing the various cognitive, psychiatric, and motor outcomes of deep brain stimulation (DBS) treatment in Parkinson's disease (PD) patients, especially the effects of stimulating the subthalamic nucleus (STN) and globus pallidus internus (GPi). For that purpose, a systematic literature search was performed through several online databases such as Google Scholar, CrossRef, and PubMed. The keywords used in the search were as follows: "Globus pallidus internus," "Subthalamic nucleus," "cognitive outcomes," "psychiatric outcomes," "Deep brain stimulation," and "Parkinson's disease." The process of screening was applied to the titles, abstracts, and full texts of the studies considered to be potentially relevant. Furthermore, the reference lists of the selected articles were thoroughly checked for any other pertinent studies (1,2).

The information found in the selected studies was summarized and extracted in many of the outcome domains, including motor symptom improvement, medication reduction, quality of life, cognitive and psychiatric outcomes, and adverse effects. Motor outcomes were grouped by the targeted nucleus that included STN, GPi, PPN, and DRT since different targets might prferably ameliorate bradykinesia, rigidity, tremor, gait, or dyskinesias. The reduction in medication was mainly assessed through the reduction in levodopa equivalent daily dose (LEDD). Cognitive and psychiatric outcomes were evaluated depending on the nucleus stimulated, the patient's perception since GPi stimulation is normally associated with fewer adverse cognitive or psychiatric effects compared to STN stimulation (3,4).

The reported adverse effects were categorized according to their severity. The low-risk complications consisted of intracranial hemorrhage and surgical site infection, whereas the moderate- to high-risk incidents included weight gain, dysarthria, and hypophonia. The limitations of the evidence were

recognized, mainly because the majority of the studies were retrospective observational designs, and the heterogeneity of the sample in terms of patients, follow-up time, and outcome measurement methods was also noted. This synthesis review intends to present an in-depth review of the existing evidence on the subject of DBS in PD, with clinical implications on the selection of the target audience and methods of counseling the patient and handling their treatment in the long term (5,6).

Inclusion criteria

The standard clinical indications for DBS were used as a basis for these studies in the case of PD only those studies which reported outcomes in patients that met the criteria for DBS were included. Patients were specifically considered good candidates for treatment if they revealed motor complications that could not be controlled with drugs, intolerance to dopamine and other agents, or tremors that did not respond to the highest dosage of the medication (LEDD >900 mg) and so on and so forth. Moreover, the patients who were being considered for the DBS had to suffer from the disease for at least 4 years, had no severe neuropsychiatric comorbidities, and had typical parkinsonism that was responsive to L-dopa.

Exclusion criteria

The research studies consisted of patients diagnosed with atypical parkinsonism showing only slight responsiveness to dopamine treatment and patients who had previously been suffering from neuropsychiatric disorders, since DBS might worsen the conditions like depression or psychosis.

Discussion

Efficacy by Parkinson's Disease Stage

Early-Stage PD

It is emerging reports that the application of deep brain stimulation (DBS) in the initial phase of Parkinson's disease might not only result in significant motor improvement but also less reliance on dopamine-based medications. Besides, early-stage intervention may postpone the occurrence of motor complications. One pilot study where STN-DBS plus optimal medical therapy was compared against medication alone showed long-term follow-up results where the reduction in medication use lasted 5 years and the economic benefits were projected to last as long as 15 years (6,7). The cognitive tests conducted on the same group of patients revealed that there were only modest declines in some specific areas like verbal fluency and processing speed over time; however, these changes could be viewed as compatible with the natural disease progression rather than being caused by DBS, as there were no major differences between early-DBS patients and controls at the five- and eleven-year assessments (8). Altogether, these results argue that early DBS may provide continuous motor benefits without bringing in any significant cognitive risk to the properly chosen patients.

Advanced-Stage PD

DBS is still giving great effects on advanced Parkinson's disease, mostly on the symptoms which the medication cannot help such as tremor, motor fluctuations and dyskinesias. Meta-analyses and long-term studies have shown the same thing again, which is the big and long-lasting motor improvements (9,10). Both STN-DBS and GPi-DBS lead to better motor scores (UPDRS III) and better daily activities in off-medication cases, with no significant differences in off-medication motor outcomes between targets (Moro et al., 2018).Improvements in quality of life are frequently observed, but several studies refer to the possibility of these perks disappearing within a span of 5 to 10 years due to the increasing severity of non-dopaminergic symptoms like axial motor and cognitive impairment (10). Therefore, DBS is still the main treatment option for advanced PD when the pharmacologic avenues have been exhausted.

Target Selection: STN vs GPi

In general, quality of life improvements is perceived. However, some studies point out that the benefits of these treatments could gradually disappear in a period of 5 to 10 years when non-dopaminergic symptoms like axial and cognitive deficits get more pronounced (11,12).

Non-Motor Outcomes

The non-motor effects of DBS have aroused interest, as these symptoms are of great concern to patients in terms of quality of life. Meta-analysis showed that there were not very significant reductions in anxiety and depression (Hedges' g = 0.34); however, it also pointed out possible declines in memory (g = –0.40), verbal fluency (g = –0.56), and executive function (g = –0.45) (12). Surprisingly enough, the early DBS-treated patients maintained equal cognitive performance with the controls during the whole study period (12).

It has been cited that on the one hand, DBS does not bring about an overall cognitive decline, but on the other hand, the physicians have to supervise the language, executive, and processing speed functions of the patients especially those getting STN stimulation. Sleep and autonomic function have been among the other non-motor areas where improvements have been noted, but their effect at the same time has been rather inconsistent, which further points out the necessity for standardized outcome assessments in future trials (13).

Factors Influencing Outcomes

DBS is highly affected by patient-specific attributes. Such factors as a baseline phenotype (tremor-dominant and akinetic-rigid), existence of dyskinesia, and non-motor symptom burden are important determinants. The timing of intervening can also make a difference, and it is possible that the earlier patients are diagnosed, the more intact neural circuitry and lower cumulative dose of dopaminergic can optimize the responsiveness and decrease the long-term use of medication (14). Accuracy of surgical techniques and accuracy of lead placement are of critical importance to efficacy, especially of axial symptoms and adverse effects. Long-term multidisciplinary follow-up and postoperative

programming also help to achieve long-lasting benefits. There is a risk of postoperative deterioration, and this can be enhanced by cognitive or mood susceptibility in the preoperative state particularly in STN targeting (14).

Limitations of Current Evidence

The DBS literature is still lacking in several aspects despite a lot of research that has been done. One of the drawbacks that has come up is the variability in the definitions of “early” and “advanced” PD between the different studies which makes comparisons difficult. Indeed, the long-term life quality in terms of nonmotor and cognitive outcomes has not been studied sufficiently, as most studies have only followed patients up to a period of 3-5 years (15).

Small and underpowered trials are characteristic of early-stage trials, and the absence of standardized stimulation protocols is another factor that hinders reproducibility (15). Very little data is available for the outcomes related to the autonomic, sleep, and caregiver areas, and economic evaluations are still rare, especially in low-resource settings. All these limitations have to be considered carefully when making decisions regarding early intervention or long-term prognosis (15).

Future Directions

The long-term efficacy and safety of Deep Brain Stimulation (DBS) in Parkinson’s disease remain an important area for further research in the future (16,17). An important area for further research for the future would be a large, prospective, multicenter study investigating long-term efficacy, safety, and quality of life outcomes related to DBS (16,17). Although in the EARLYSTIM trial, it was found that DBS was effective in patients with early motor complications, and it did not lose its efficacy with time, randomized long-term studies are needed for further investigation of differences in outcomes between early vs. late initiation of DBS therapy. An important long-term outcome of DBS, which needs to be measured in further study, would be the improvement in quality of life (18).

There needs to be a focus in the future on developing ways for optimal patient selection. A key area that needs to be completely understood in relation to prognostic potential for neuroimaging, as well as genes in determining potential responders and non-responders, remains a challenge in the use of DBS. "Surgicogenomics" and imaging lead placement for improved surgical outcomes are key areas that need to be explored in the future (19). In addition, comprehensive understanding of the nature of monogenic mutations for LRRK2, PRKN, SNCA, and GBA has become an important area, as it has been seen that there has been a variation in the benefit of DBS in patients with different mutated genes. On the other hand, patients undergoing DBS with SNCA and possibly other genes like GBA can affect the benefit of DBS since there has been progression of cognitive and neuropsychiatric changes. Technological advancements are providing the way for personalized DBS approaches (19,20). New hardware innovations and sophisticated programming techniques are still being explored as areas of research. These also encompass methods of adaptive DBS (aDBS) and closed-loop stimulation wherein adjustments of stimulation parameters are underway, to be made in real-time to maximum advantage at minimum side effects (20).

There also has to be a widening of research aims into additional, traditional, appendicular motor manifestations of PD due to a need for further investigation of amelioration of non-motor symptoms of PD and cognitive safety of DBS treatment recipients. Further advancements in DBS technology should relate to improvement of those non-treatable manifestations of PD that affect the axis of the body, including, for example, voice, balance, and walking (21). This, in particular, does not improve as well as other appendicular manifestations of PD and, in some cases, can even deteriorate as a result of surgical and electrical treatments of PD as DBS. The current concern, presently in investigation in a DBS-MODE study, regards improvement of cognitive safety, due to which DBS in patients with severe cognitive deficiency has been thus far withheld (21).

Lastly, future directions ought to take into consideration the cost-effectiveness as well as access associated with this particular therapy approach. The underutilization of DBS has occurred partly due to myths about DBS risks and benefits for patients with PD. Studies assessing how early vs. late interventions with DBS affect costs from a healthcare perspective are needed. Methods of increasing access to this therapy approach in different healthcare systems ought to involve adopting telemedicine, which would help those in distant areas (22,23).

Conclusion

This narrative review not only summarizes the existing evidence but also provides an overview of the role of the deep brain stimulation (DBS) in Parkinson's disease continuum by focusing on its established efficacy at taking over motor symptoms control, reduction of medication, and providing better quality of life for specifically chosen patients. Choosing disease stages, STN or GPi deep brain stimulation consistently brings about the considerable and lasting reduction of tremors, stiffness, slowness of movement, motor fluctuations, and involuntary movements when drug treatments become inadequate or poorly tolerated. Timing of the intervention is, thus, probably the most important factor determining the outcome. Presence of early-intervention studies suggests that DBS applied after the start of motor complications but before the advanced disease-related cognitive or axial disabilities can result in maintenance of motor benefits, reduction of long-term dopaminergic burden, and cognitive safety in meticulously chosen patients.

Deep brain stimulation (DBS) remains a very effective method whenever the severe form of Parkinson's disease is treated, and also as a last resort in the cases of patients whose movement problems are unresponsive to any other treatment. Yet, the non-dopaminergic aspects like gait and balance problems, as well as cognitive decline, are constantly the ones determining the patient’s long-term progress. The disparity in stimulation sites accentuates the requirement for personalized treatment plans where STN-DBS provides more reduction in medication but may have the downside of higher cognitive or psychiatric risk, similarly the GPi-DBS shows a better neuropsychiatric profile for patients prone to such risks. The non-motor outcomes are still mixed, which underlines the need for thorough

preoperative evaluation, realistic discussions with patients, and continuous teamwork of different specialists throughout the patient's life.

Nevertheless, despite the strong evidence that supports DBS, there are still significant gaps such as the lack of long-term data about the outcomes of the no motores and quality of life, as well as the absence of standard protocols of stimulation and assessment. Futuristic studying should be used to enhance the quality of the therapy through the usage of the latest techniques possible. It would then entail including larger and more accurate multicenter studies comparing early and late DBS, to refine patient selection methods using neuroimaging and genetic biomarkers, and to test new technology such as adaptive and closed-loop stimulation. There will also be the need to combat underutilization and ensure that there is equal access through cost-effectiveness, accessibility, and health system integration. To sum up, despite the fact that DBS continues to be a cornerstone therapy in the management of Parkinson disease, its optimum application will rely on the time of intervention being right, the selection of the target, and current advances in precision neuromodulation.

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