Research Article

A review on Parkinson's disease symptoms before and after deep brain stimulation treatment

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Received - 22 September 2022 Initial Review - 19 October 2022 Accepted - 01 November 2022

ABSTRACT

Introduction: Parkinson's disease (PD), followed by Alzheimer's disease, is the most common progressive neurodegenerative disease. Tremors, rigidity, akinesia, and disorders are common PD symptoms. Over the last few decades, deep brain stimulation (DBS) of the subthalamic nucleus has become a standard treatment for advanced PD. The aim of this systematic review paper is to see the difference between the symptoms of PD before and after DBS. **Methods:** We conducted a literature search using PubMed and Google Scholar. We chose research from the past 10 years. We retrieved 64 papers, and seven duplicated papers were removed. We reviewed the abstract for the remaining 57 papers which led to the selection of 29 papers. After applying inclusion and exclusion criteria for the remaining 29 papers, 23 papers in the English language were chosen for our review. **Results:** Five Randomized Clinical Trials (RCTs) studied the outcomes of DBS and eight RCTs about effects on posture and motor function. Four RCTs investigated the effects on gait and balance, two on tremors, and the remaining two on posture. The effects of DBS on speech and language were compared in two RCTs. Three studies looked at cognitive performance. One RCT studied sleeping versus awake DBS on PD. These studies showed that with DBS treatment, there was significant improvement in posture, motor function, gait, balance, speech, and language. However, more studies are required for the further analysis on dysphagia and urinary dysfunction. **Conclusion:** Our study contributed to a better understanding of the advantages of DBS for a range of symptoms, but it concluded that additional RCT on dysphagia and urinary dysfunction was required to reach a reliable conclusion. More research is required to determine the effects of DBS on different motor and non-motor PD symptoms to standardize treatment.

Key words: *Parkinson's disease, Deep brain stimulation, Dyskinesias*

Parkinson's disease (PD) is the most common progressive neurodegenerative disease, followed by Alzheimer's disease, and public concern about PD is growing. Tremors, rigidity, akinesia, and disorders are common PD symptoms [1]. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has become a standard treatment for advanced PD over the past few decades, with >50% improvement in the unified PD rating scale part III (UPDRS III) scale in prospective randomized trials and up to 60% in a retrospective study [2]. Subthalamic nucleus DBS (STN-DBS) has been shown to improve quality of life (QOL) and motor function in people with advanced PD who have severe motor fluctuations and dyskinesia. STN-DBS has recently been shown to improve QOL and motor function in people with early-stage PD [3]. DBS was hypothesized to "inhibit activity" in the target because its effect matched rate-based models of basal ganglia circuits [4]. The evidence, however, shows that stimulation has a variety of effects on different neuronal elements in and around the STN, leading to therapeutic improvement [5]. This finding has clinical implications for the Parkinson's community because it implies that people with early-stage PD who receive standard pharmacological therapy are 5 times more likely to have worse rest tremors over the course of 5 years than those who receive STN DBS. This finding implies that, in addition to slowing the progression of rest tremor, early STN DBS intervention provides long-term symptomatic rest tremor benefits when compared to standard medical therapy [6]. The majority of cognitive test scores showed no significant changes 3 and 12 months after STN-DBS. Assessments of verbal fluency, processing speed, and attention/working memory, on the other hand, showed reductions [7]. Despite its positive effects on QOL and motor control, STN DBS has the potential for adverse effects including temporary decreases in cognition [8]. Although STN DBS can affect memory, attention, and executive skills, verbal fluency is the most persistent reduction [9]. The purpose of this study was to compare the clinical characteristics of people before and after STN-DBS.

METHODS

For the pertinent published research, we carried out a thorough literature search using PubMed and Google Scholar. We used the terms "Parkinson's illness, DBS, and outcome" both singly and

collectively. We chose studies from the previous 5 years. Table 1 lists the outcomes for each search keyword. 57 of these research papers were shortlisted after reading the abstracts, and 29 were chosen based on the significance of their titles. We used the inclusion and exclusion criteria, eliminated duplicate papers, and only chose English-language full-text papers. Finally, 23 research publications in all were included in this review (Fig. 1). For the introduction and discussion parts, a few other supplementary references were also taken into consideration. Cochrane risk bias of the tool was used to assess the quality of the papers. Table 2 elaborates on the studies that were included is the present systematic review.

Criteria for Inclusion and Exclusion

The review included randomized clinical trials (RCTs) that had been published within the previous 5 years. These RCTs investigated the effects of DBS on patients with different symptoms of PD. This analysis only included papers that were based on RCTs. In this review report, all RCTs that passed the Cochrane evaluation tool were chosen. Studies that were not published in English were not included in the study. In addition, omitted were editorials and non-RCTs.

Table 1: Keyword search by database

Regular searches	PubMed
Parkinson's disease	131,104
Deep brain stimulation	17,769
Parkinson's disease and DBS	7,687
Parkinson's disease and DBS and outcome	86

DBS: Deep brain stimulation

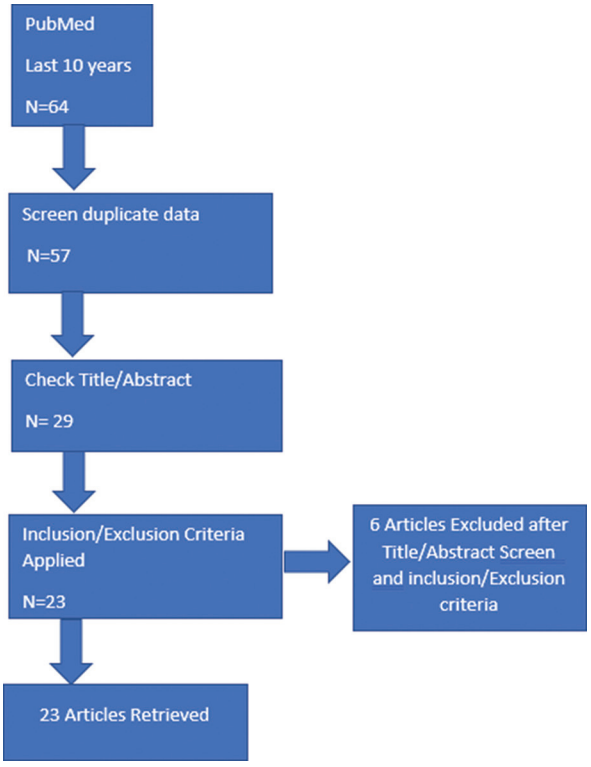

Figure 1: Methodology and article selection process

RESULTS

Five of the 23 RCT research papers that were chosen were the outcomes of RCTs that used DBS to treat PD for a predetermined amount of time [3,6,8,10,11]. Eight RCTs described the beneficial effects on posture and motor function. Out of the eight RCTs, four examined how DBS affected gait and balance, two examined tremors, and the remaining two described how DBS affected posture. The effects of DBS on speech and language disability were compared in two RCTs. There were three articles that discussed how DBS and PD affected cognitive performance. One RCT compared the effects of DBS during sleep versus awake on PD. The effects of dysphagia with DBS were discussed in the other two RCTs. All research publications written about this population and published <10 years ago were included in all RCTs. Table 2 displays several studies from the study included in this review article.

DISCUSSION

For individuals with PD who experience bothersome motor fluctuations and dyskinesias that are resistant to the most effective medication treatment, DBS has proven itself as a viable therapeutic option [1]. There are various results for PD symptoms with DBS treatment.

Outcome of DBS

Numerous studies have shown that DBS is more effective than conventional medication in improving PD symptoms and indications. The papers in question ranged in sample size from 26 to 124 and covered the years 2012 to 2020. The primary endpoint in each of these studies was the improvement of PD symptoms [3,6,8,11,12]. By the age of 11, stimulation had reduced motor symptoms by 35.8% when compared to the pre-operative off-state. Motor difficulties were significantly under control, with an 84.6% improvement in dyskinesias and a 65.8% improvement in motor fluctuations [11]. In 2018, 25 people with PD were randomly assigned to either best medical care or caudal zona incerta (cZi) DBS. Blomstedt *et al*. concluded that, when compared to baseline, the DBS group's UPDRS-III scores were 41% higher off-medication and during stimulation than those of the non-surgical patients. There were no differences between the groups in the on-medication condition at either the baseline or the 6-month mark [12]. Furthermore, the decrease in PDQ-39-SI after 24 months was associated with PDQ-39-SI at baseline in both therapy groups ($p<0.05$). The greater the improvement in QOL after 24 months, the lower the baseline QOL (higher score). There was no association found for any other baseline traits examined in either therapy group [3]. Hacker *et al*., on the other hand, found that at baseline, every patient had the highest freezing of gait (FoG) score possible, demonstrating that FoG is always present when walking. At the end of the study, the prevalence of FoG in combined stimulation of substantia nigra pars reticulata and STN, was "never" (in one patient), "very rarely or once a month" (in one

Table 2: Details of few studies that were included in the present paper

Author	Year of publication	No. of patients	Purpose of study	Intervention	Result/conclusion
Rizzone *et al*. [11]	2014	26	To present the findings from a lengthy follow-up (mean 11 years, range 10–13) on 26 patients who had bilateral implants at two centers	RCT	The existence of REM behavior disorder at baseline, age at disease beginning, and axial subscore in off-condition were discovered to be related with a higher chance of acquiring impairment over time
Blomstedt *et al*. [12]	2018	25	This study's objective was to assess the impact of cZi DBS on Parkinson's disease patients (PD)	RCT	Only in the DBS group did the PDQ-39 domains "stigma" and "ADL" show improvement. In both groups, the PDQ-39 summary index increased
Schuepbach *et al*. [3]	2019	n=124STN-DBS best medical treatment (n=127)	To look into the factors that influence the illness-specific quality of life (QOL) of Parkinson disease (PD) patients with early motor problems who get deep brain stimulation (DBS) of the subthalamic nucleus	RCT	The most significant indicator of benefit in individuals with PD and early motor problems is impaired QOL, as subjectively assessed by the patient, satisfying the gold standard inclusion criteria for STN-DBS
Hacker *et al*. [6]	2020	28	To present the results of a pilot clinical trial using deep brain stimulation in early-stage Parkinson disease (PD) at the 5-year mark	RCT	Early STN DBS+ODT individuals had 0.21 times the odds of experiencing worse rest tremor compared to early ODT participants (p=0.001, OR 0.21, 95% CI 0.09–0.45)
Weaver *et al*. [8]	2012	GPi (n=89) STN DBS (n=70)	In a multicenter randomized controlled trial, our goal was to examine the long-term effects of deep brain stimulation of the globus pallidus interna (GPi) and subthalamic nucleus for patients with PD		The progression of the underlying disease is likely reflected in the steady decline in neurocognitive function and slight declines in quality of life after initial improvements, which emphasizes the significance of nonmotor symptoms in assessing quality of life

patient), "rarely or once a week" (in one patient), or "continuous" (three patients) [6]. All of the therapies improved daily living activities [6]. Both the stimulation and control groups in Weaver *et al*. randomized trial experienced similar neuropsychological changes. Only the stimulation group lost letter verbal fluency in the Stroop task, while both groups lost category and switching verbal fluency. Depression symptoms improved in both groups, but more frequently in the stimulation group [8].

Camptocormia

Camptocormia is defined as an unintentional anterior flexion of the thoracolumbar spine of at least 15 while standing or walking, which can be reversed by sleeping in a recumbent position [13,14]. Liang *et al*. studied 15 camptocormia patients with PD (7 men) who underwent bilateral STN DBS as part of the study cohort. Following DBS surgery, all research participants' symptoms improved, although to varying degrees. The lowest and highest rates of improvement were 20% and 100%, respectively. Both the movement disorder society-unified PD rating scale III item 3.13 score and the degree of camptocormia improved significantly ($p<0.05$) [1]. Patients with PD aged 50–75 years were randomly assigned to either optimal drug therapy (ODT) or DBS plus ODT (DBS + ODT) for 6 months to 4 years. At baseline, 6, 12, 18, and 24 months, all patients discontinued all PD therapy for 1 week. The UPDRS-III "off" item scores were compared between the ODT and DBS + ODT groups (n=28). Patients who received ODT were worse in UPDRS-III "off" rest tremor rating from baseline to 24 months (p=0.002). From baseline to 24 months, rest tremor slopes favored DBS + ODT both "off" and "on" therapy (p=0.001 and p=0.003, respectively). DBS may slow the progression of rest tremor in early PD, according to these findings [16]. More research is needed before concluding that DBS improves camptocormia over time.

Tremors

According to Hacker *et al*., patients receiving ODT compared to DBS + ODT had worse "off" rest tremor score changes from baseline to 24 months (p=0.002). Rest tremor slopes favoring DBS + ODT both "off" and "on" therapy ($p<0.001$ and p=0.003, respectively) from baseline to 24 months. In comparison to patients undergoing DBS + ODT, more ODT patients experienced new rest tremor in previously unaffected limbs (p=0.001) [15]. In comparison to the preoperative off-state, stimulation considerably reduced the motor symptoms by 35.8% by the age of 11. With an

84.6% improvement in dyskinesias and a 65.8% improvement in motor fluctuations, motor difficulties were substantially under control. In spite of this, the UPDRS-II-on score declined by 88.5%, primarily due to the deterioration of symptoms that were poorly responsive to levodopa [16].

Gait and Balance

PD patients who had reported gait changes and had received post bilateral subthalamic DBS for at least 3 months. Following a baseline assessment, subjects were randomly allocated to 60 or 130 Hz stimulation while all other metrics remained constant. Each subject was set at each frequency twice, with a 60-min stimulation interval between each gait evaluation. In terms of the primary outcome measure of stride length, there was no statistically significant difference between the two frequencies. Even though patients reported a statistically significant improvement in gait, there was a statistically significant difference in outcomes. Furthermore, at 60 Hz, there was less tremor control [17]. Similarly, in a 2015 study, with stride length as the main outcome measure, there was no discernible difference between the two frequencies. A considerable subjective improvement in their gait was reported by two of the 20 patients, although there was no statistically significant difference in their outcomes [18]. In comparison to the off state, balance scores increased with DBS turned on, and scores increased even more with medication. In comparison to the STN group, the Globus Pallidus interna (GPi) group demonstrated enhanced performance in the post-surgery off state and higher evaluations of balance confidence [19]. PD patients who get STN-DBS have improved levodopa responsive cardinal symptoms and decreased motor fluctuation and dyskinesia [20-24]. In addition, when compared to 130 Hz, the 60-Hz stimulation significantly reduced the FOG measured by the subjective questionnaire ($p<0.05$) and objective freezing spells on the SWS test, the axial symptoms ($p<0.001$), and total Parkinsonian motor symptoms in UPDRS-III ($p<0.01$) (60 vs. 130 Hz) [25].

Speech and Language

Six months after surgery, cZi stimulation was found to decrease spontaneous speech intelligibility on a group-level relative to no stimulation (8 adverse, 1 positive, and 2 no change). Adverse consequences of cZi-DBS were rarely seen 12 months after surgery (2 positive, 3 adverse, and 6 no change). The pre-operative administration of l-dopa as a component of the DBS operation evaluation resulted in the best overall treatment outcome (1 adverse, 4 positive, and 6 no change) [26]. In contrast to both controls and patients taking only drugs, who did not differ from one another across assessment sessions, STN-DBS enhanced naming of manipulated (motor) but not non-manipulated (non-motor) objects. However, compared to the other two subject groups, who once more did not differ, STN-DBS resulted in inferior performance at regulars (grammar), but not irregulars (lexicon). According to the findings, STN-DBS has a detrimental effect on language in the early stages of PD; however, this effect may be more focused on lowering grammatical than lexical processing [27].

Urinary Dysfunction and Dysphagia

DBS treatment significantly reduced the symptoms of urinary dysfunctions in PD patients, including urine frequency, urgency, and incontinence ($p<0.05$), Female PD patients' AUA-SI, urinary symptom scores, and QOL significantly improved after DBS surgery when compared to those in male patients ($p<0.05$), as did other functional indicators of the urinary tract, such as the maximum urinary flow rate, detrusor pressure at peak flow, and residual urine volume [28]. In both STIM OFF and both DBS settings, PD patients had considerably more pharyngeal residues than healthy controls. In comparison to STN+DBS, simultaneous STN + SNR stimulation demonstrated no further beneficial effects on objective dysphagia and self-reported swallowing function [29].

Cognition

When compared to baseline, all three verbal fluency tests showed a substantial deterioration at 12 months ($p<0.001$). About 31% of patients experienced decline in letter fluency, 36% experienced decline in category fluency, and 43% experienced decline in switching fluency [30]. The results of resting state functional magnetic resonance imaging and the major cognitive outcomes both showed no discernible improvements. In comparison to sham stimulation (12 points [range, 8–38 points]; median difference, 5 points; 95% CI, 2.5–8.5 points; $p=0.03$) and the pre-operative baseline (13 points [range, 5–25 points]; median difference, 2 points; 95% CI, 8 to 5.5 points; $p=0.69$), nucleus basalis of meynert (NBM) DBS resulted in higher neuropsychiatric inventory scores (8.5 points [range, 4–26 points] [31]. Depression significantly decreased in participants with unilateral STN DBS at 6 months after surgery (4.94 ± 4.02) compared to pre-operative baseline (7.90 ± 4.44 with $p=0.0001$. At any time, there was no correlation between Hamilton depression rating score (HAMD-17) scores and UPDRS part III. It is interesting to note that at baseline, 3 months, and 6 months after surgery, the HAMD-17 is substantially linked with sleep quality and quality of life. Over the same time period, HAMD-17 did not significantly change in participants without DBS. Unilateral STN DBS helps improve depression in PD patients 6 months after surgery. Depression improves over time and equates with better sleep and the quality of life [31].

CONCLUSIONS

DBS of the STN is now the standard treatment for people with severe PD. In our review study, we compared various PD symptoms before and after treatment. When we compared ODT+DBS to the best medication therapy for tremors, we saw that the tremors improved significantly. DBS stimulation, like GPi, resulted in greater improvement. STN-DBS enabled the

naming of motor-manipulated but not non-motor-manipulated objects. The urinary frequency and functional state of dysphagia both improved. More research on dysphagia and urinary dysfunction will be required to reach more precise conclusions. In participants receiving unilateral STN-DBS, ratings on the neuropsychiatric inventory increased after NBM DBS, and depression was significantly lower than at baseline. Our study aided in understanding the benefits of DBS for a variety of symptoms, but it concluded that additional RCT on symptoms such as dysphagia and urinary dysfunction were required to obtain a reliable conclusion. Other symptoms such as loss of smell, constipation, soft voice, and so on were not addressed in our review article. More research is needed to determine the effects of DBS on various motor and non-motor PD symptoms so that treatment can be standardized if it is found to be effective.

REFERENCES

1. Liang S, Yu Y, Li H, *et al*. The study of subthalamic deep brain stimulation for Parkinson disease-associated camptocormia. Med Sci Monit 2020;26:e919682.
2. Engelhardt J, Caire F, Damon-Perrière N, *et al*. A phase 2 randomized trial of asleep versus awake subthalamic nucleus deep brain stimulation for Parkinson's disease. Stereotact Funct Neurosurg 2021;99:230-40.
3. Schuepbach WM, Tonder L, Schnitzler A, *et al*. Quality of life predicts outcome of deep brain stimulation in early Parkinson disease. Neurology 2019;92:e1109-20.
4. Kahan J, Urner M, Moran R, *et al*. Resting state functional MRI in Parkinson's disease: The impact of deep brain stimulation on 'effective' connectivity. Brain 2014;137:1130-44.
5. Vedam-Mai V, van Battum EY, Kamphuis W, *et al*. Deep brain stimulation and the role of astrocytes. Mol Psychiatry 2012;17:124-31, 115.
6. Hacker ML, Turchan M, Heusinkveld LE, *et al*. Deep brain stimulation in early-stage Parkinson disease: Five-year outcomes. Neurology 2020;95:e393-401.
7. Okun MS, Gallo BV, Mandybur G, *et al*. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: An open-label randomised controlled trial. Lancet Neurol 2012;11:140-9.
8. Weaver FM, Follett KA, Stern M, *et al*. Randomized trial of deep brain stimulation for Parkinson disease: Thirty-six-month outcomes. Neurology 2012;79:55-65.
9. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ 2009;339:b2535.
10. Rothlind JC, York MK, Carlson K, *et al*. Neuropsychological changes following deep brain stimulation surgery for Parkinson's disease: Comparisons of treatment at pallidal and subthalamic targets versus best medical therapy. J Neurol Neurosurg Psychiatry 2015;86:622-9.
11. Rizzone MG, Fasano A, Daniele A, *et al*. Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: From the advanced phase towards the late stage of the disease? Parkinsonism Relat Disord 2014;20:376-81.
12. Blomstedt P, Persson RS, Hariz GM, *et al*. Deep brain stimulation in the caudal zona incerta versus best medical treatment in patients with Parkinson's disease: A randomised blinded evaluation. J Neurol Neurosurg Psychiatry 2018;89:710-6.
13. Djaldetti R, Mosberg-Galili R, Sroka H, *et al*. Camptocormia (bent spine) in patients with Parkinson's disease--characterization and possible pathogenesis of an unusual phenomenon. Mov Disord 1999;14:443-7.
14. Abe K, Uchida Y, Notani M. Camptocormia in Parkinson's disease. Parkinsons Dis 2010;2010:267640.
15. Hacker ML, DeLong MR, Turchan M, *et al*. Effects of deep brain stimulation on rest tremor progression in early stage Parkinson disease. Neurology 2018;91:e463-71.
16. Valldeoriola F, Muñoz E, Rumià J, *et al*. Simultaneous low-frequency deep brain stimulation of the substantia nigra pars reticulata and high-frequency stimulation of the subthalamic nucleus to treat levodopa unresponsive freezing of gait in Parkinson's disease: A pilot study. Parkinsonism Relat Disord 2019;60:153-7.
17. Phibbs FT, Arbogast PG, Davis TL. 60-Hz frequency effect on gait in Parkinson's disease with subthalamic nucleus deep brain stimulation. Neuromodulation 2014;17:717-20; discussion 720.
18. St George RJ, Carlson-Kuhta P, Nutt JG, *et al*. The effect of deep brain stimulation randomized by site on balance in Parkinson's disease. Mov Disord 2014;29:949-53.
19. Deuschl G, Schade-Brittinger C, Krack P, *et al*. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006;355:896-908.
20. Weaver FM, Follett K, Stern M, *et al*. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: A randomized controlled trial. JAMA 2009;301:63-73.
21. Follett KA, Weaver FM, Stern M, *et al*. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med 2010;362:2077-91.
22. Williams A, Gill S, Varma T, *et al*. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): A randomised, open-label trial. Lancet Neurol 2010;9:581-59.
23. Schuepbach WM, Rau J, Knudsen K, *et al*. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368:610-22.
24. Xie T, Vigil J, MacCracken E, *et al*. Low-frequency stimulation of STN-DBS reduces aspiration and freezing of gait in patients with PD. Neurology 2015;84:415-20.
25. Sandström L, Hägglund P, Johansson L, *et al*. Speech intelligibility in Parkinson's disease patients with zona incerta deep brain stimulation. Brain Behav 2015;5:e00394.
26. Phillips L, Litcofsky KA, Pelster M, *et al*. Subthalamic nucleus deep brain stimulation impacts language in early Parkinson's disease. PLoS One 2012;7:e42829.
27. Zong H, Meng F, Zhang Y, *et al*. Clinical study of the effects of deep brain stimulation on urinary dysfunctions in patients with Parkinson's disease. Clin Interv Aging 2019;14:1159-66.
28. Pflug C, Nienstedt JC, Gulberti A, *et al*. Impact of simultaneous subthalamic and nigral stimulation on dysphagia in Parkinson's disease. Ann Clin Transl Neurol 2020;7:628-38.
29. Tröster AI, Jankovic J, Tagliati M, *et al*. Neuropsychological outcomes from constant current deep brain stimulation for Parkinson's disease. Mov Disord 2017;32:433-40.
30. Gratwicke J, Zrinzo L, Kahan J, *et al*. Bilateral deep brain stimulation of the nucleus basalis of meynert for Parkinson disease dementia: A randomized clinical trial. JAMA Neurol 2018;75:169-78.
31. Birchall EL, Walker HC, Cutter G, *et al*. The effect of unilateral subthalamic nucleus deep brain stimulation on depression in Parkinson's disease. Brain Stimul 2017;10:651-6.

Funding: None; Conflict of Interest: None Stated.

How to cite this article: Maharjan R, Sambandam R. A review on Parkinson's disease symptoms before and after deep brain stimulation treatment. Eastern J Med Sci. 2022;7(3):64-68.

DOI: 10.32677/ejms.v7i3.3640