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Effects of subthalamic deep brain stimulation on treating motor symptoms in early Parkinson's disease

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ABSTRACT

Objective: Assess the efficacy of subthalamic nucleus deep brain stimulation (STN DBS) versus solely optimal pharmacological use in early Parkinson's Disease to improve motor dysfunction. **Design:** Systematic Literature Review. **Methods:** Searches were completed on PubMed utilizing the MeSH terms: "subthalamic, deep brain stimulation, and early parkinson." Using PubMed the following limits and terms were used: published in the last 10 years, randomized controlled trial, English, human, and removing duplicates. A total of three studies resulted after the search. **Results:** All three studies showed statistically significant results in reduction in disease progressive motor symptoms. Additionally, at the end of each study a lower dosage of levodopa was needed to control symptoms. **Conclusion:** STN DBS shows promising improvements in PD motor symptoms; however, the choice to undergo this treatment must be an individual conversation for each patient and their provider with a risk versus benefit analysis on a case-by-case basis. Further research is needed with great sample sizes and to assess long-term effects of STN DBS on patients with PD as the therapy is implemented years earlier than currently approved.

INTRODUCTION

Parkinson's disease (PD) is a disabling, incurable neurodegenerative disorder that impacts the dopaminergic neurons in the substantia nigra.[1] The main motor symptoms characteristic of PD include bradykinesia, tremor, and rigidity. Additional motor symptoms include cramping, drooling, dyskinesias, festination, masked facial expressions, micrographia, and shuffling gait. While there is constant research being conducted on this disease, the pathophysiology of PD is still not completely understood. PD is characterized by the death of dopaminergic neurons in the substantia nigra pars compacta. The buildup of alpha-synuclein proteins that make up Lewy bodies are thought to be the cause of the dopaminergic neuron death.[2] The substantia nigra pars contracta produces and uses the neurotransmitter dopamine to send signals to the basal ganglia, which allows for controlled, voluntary movements. With the death of the neurons that produce dopamine, the function of the basal ganglia is hindered, thus causing the many motor symptoms seen in PD.[2]

Treatment for PD is a challenging feat. As of now, there are no treatments that reverse or cure the disease process of PD. The purpose of treatment is to manage symptoms in order to improve quality of life. Management requires polypharmacy as the disease progresses and more symptoms appear. Additionally, tolerance to medications, like levodopa, require higher doses or different combinations of medications to produce a similar effect.[1] Current first-line pharmacological treatments like levodopa tend to help motor symptoms, but also cause unwanted side effects, which can be significant and debilitating.[3,4]

Deep brain stimulation (DBS) is a newer breakthrough that offers a different approach than pharmacotherapy in the treatment of PD; however, it is not disease modifying long term. DBS is commonly called the "pacemaker of the brain". Magnetic resonance imaging and cell electrical activity is used to guide electrode placement into particular areas of the brain responsible for the abnormal motor symptom activity. Subsequently, an implantable pulse generator (IPG) is inserted either under the collarbone or in the abdomen, which provides an electrical impulse to those motor areas in the brain. Currently, the brain is mainly targeted in two

areas with DBS: the subthalamic nucleus (STN) and the globus pallidus interna (GPi), both of which have FDA approval for PD. The electrical impulse from DBS interrupts the nerve impulses at the damaged areas of the brain that cause PD symptoms, such as tremor. Tremor was the first symptom to show improvement with DBS in 1997. In 2002, DBS was recognized for treatment in advanced PD. DBS was permitted for the initial stages of PD in 2016, but is still heavily controversial and not well studied.[5] Given the favorable effect DBS has on motor symptoms of PD, this literature review investigates whether DBS in the STN is effective in early stage PD to decrease these motor symptoms.[5]

Clinical question: Do patients with early PD who receive STN DBS versus only optimal drug therapy have a slower progression of motor dysfunction?

METHODS

An initial search of PubMed was conducted in September 2020 using the search terms "Subthalamic brain stimulation in early Parkinson's Disease." Three hundred and sixty two articles were found with the absence of any duplicates. These articles were screened for eligibility. One hundred and sixty of these articles were excluded as the studies were not conducted on human subjects. Another 183 studies were excluded as they were not randomized control trials. This left 19 full-text articles for further assessment. Articles were excluded if they did not answer the clinical question, did not include motor symptom related results, or were pilot studies to one of the three articles chosen (Figure 1). Three studies qualified for this research.

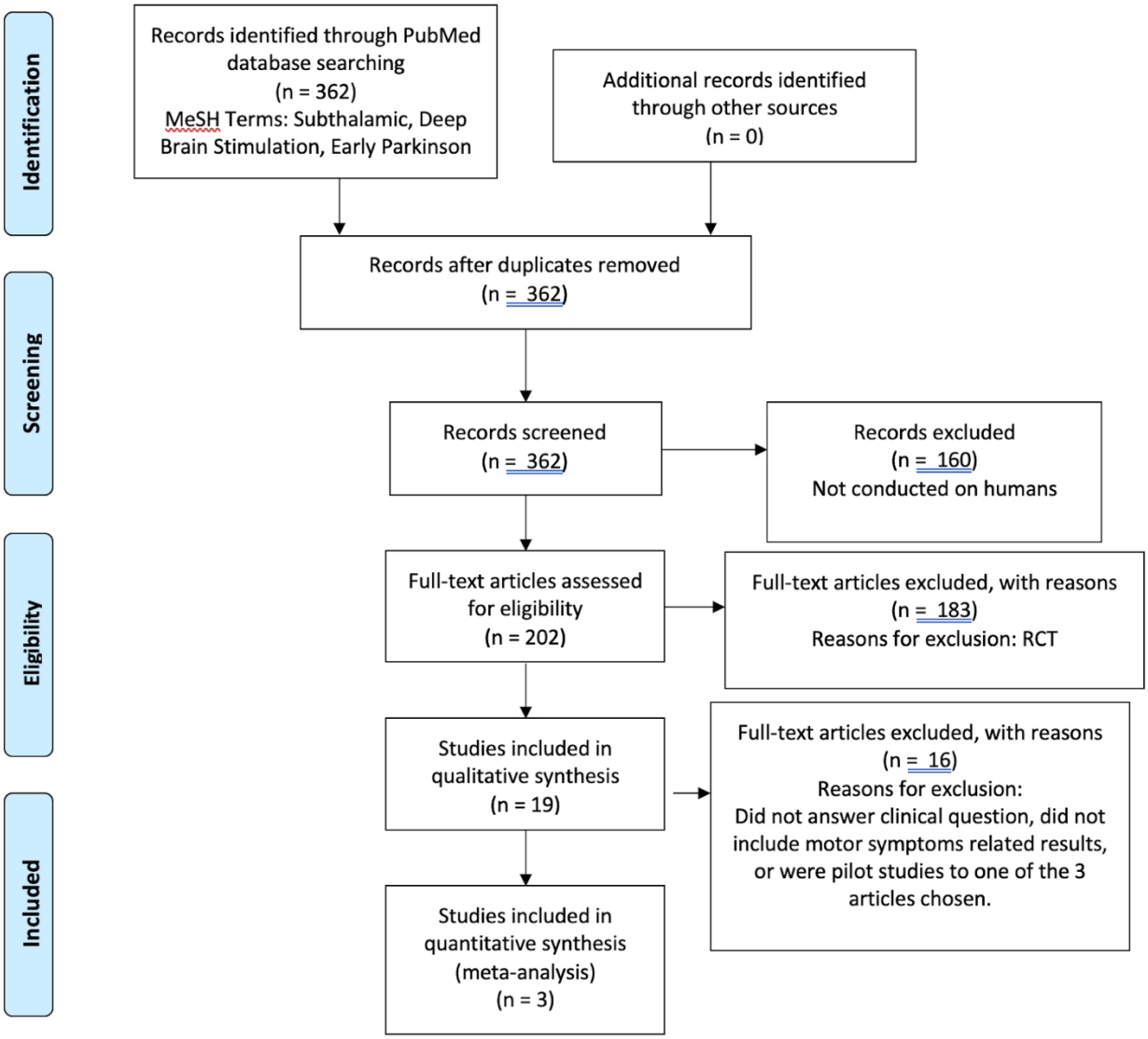

Figure 1. PRISMA Flow Diagram

RESULTS

Study #1

Effects of Deep Brain Stimulation on Rest Tremor Progression in Early Stage Parkinson Disease (2018)

Study Objective: To assess the progression of motor symptoms in PD patients with early DBS therapy. [6]

Study Design:

This pilot study was a prospective, randomized, controlled, single-blind study for PD patients who are 50-75 years old. It was sponsored by and researched at Vanderbilt University. Thirty participants were registered in the research study, but only 28 participants lasted the

whole trial. Two participants left the study early: one dropped out and the other did not meet inclusion criteria for the history of PD medications. Both participants were in opposite groups. All patients had a Hoehn & Yahr score of II while "off" medication time and a history of taking PD medications for six months to four years. The Hoen and Yahr (HY) Scale is used to define early and advanced PD in research. Stage 1 includes unilateral involvement only with limited or no functional disability. Stage 2 consists of bilateral or midline involvement without impairment of balance. Stage 3 is comprised of bilateral disease, mild to moderate disability with impaired postural reflexes, and physical independence. Stage 4 includes severely disabling disease and still able to walk or stand unassisted. Stage 5 is defined as confinement to bed or wheelchair unless aided. Classically, HY Stages 1 and 2 are defined as early, Stage 3 as moderate, and Stages 4 and 5 as late disease.[7] Other participant demographics were noted to be similar amongst the group. The participants could not have a history of dyskinesia or motor symptoms to be enrolled in the study.[6]

On day one of the trial each patient was videoed while "on" medication and outcomes were measured via the UPDRS-III (Unified Parkinson's Disease Rating Scale) scale for a baseline evaluation. Eight days later, after a washout period, the patients were videoed while "off" medication. At the conclusion of the baseline evaluations, participants were randomized into groups for either ODT (optimal drug therapy) or bilateral STN DBS & ODT. Every follow-up visit consisted of a video recording on day one "on" therapy and on day eight "off" therapy after a washout period. All follow-ups were conducted in the center every six months throughout the two years of research. At baseline and at the end of the study each participant was evaluated for how many body parts were affected by a resting tremor. New development of a resting tremor was distinguished by limb.[6]

The STN DBS & ODT group was not actively treated until approximately 1.5 months after baseline testing because of preparing for pre-op and post-op recovery. After surgery, each patient receiving STN DBS were titrated to the efficacious dose, which took about four weeks. In this trial the frequency and pulse width was set at 60 μs and 130 Hz using monopolar stimulation (model 3389 leads; Medtronic, Minneapolis, MN). All patients were assigned a neurologist that individually managed their medications. Both groups got levodopa as their standardized medication. The doses of levodopa given were individualized.[6]

After the conclusion of the trial a private, blinded neurologist, who was certified in scoring UPDRS, watched all the unlabeled videotapes and graded each patient. The neurologist reported the UPDRS-III score which included all of the motor tests, but not rigidity because it cannot be rated through video.[6]

After the trial a patient satisfaction survey was given to confront any experiences and assess level of satisfaction. Twenty-seven participants finished the questionnaire, 14 from the ODT group and 13 from the STN DBS & ODT group. The STN DBS & ODT group got supplementary questions to assess their impression of DBS .[6]

The statistical data was analyzed by using IBM SPSS Statistics 23.0. Using Bonferroni comparisons from a Wilcoxon rank-sum test, p was found to be <0.0038 and therefore considered to be statistically significant. Numerous linear regression models were generated with approximating variance and equations to assess the trend over two years for both groups. Separate data analyses were made when patients were "on" and "off" therapy. To discover the p-value for each group, the study used two degrees of freedom for the Chi squared test of the null hypothesis. The study calculated the hazard ratio between both groups by using the Cox proportional hazard model and binary terms for the treatment group. This hazard ratio assessed

the time until the UPDRS-III score for "off" rest tremor worsened by two points on the scale. A p-value for the between-group difference was then found via a log-rank test. At baseline and at the end of the study each participant was evaluated for how many body parts were affected by a resting tremor. New development of a resting tremor was distinguished by limb and statistically analyzed by using a 2-sample t-test with variances that are equivalent. The Fisher exact test was applied to find the difference between the development of resting tremor versus no development of a resting tremor. In this study $p < 0.05$ is considered to be statistically significant.[6]

Study Results:

At baseline the STN DBS & ODT group had a lower daily dose of levodopa and worse "on" therapy scores for the UPDRS but neither of these things made a statistically significant difference. The "off" therapy versus the "on" therapy scores declined for both groups. The only "off" therapy score that reached statistical significance on the UPDRS-III score ($p=0.002$) between groups was the rest tremor "off" scores by 3.1 points better in the DBS & ODT group. The worsening resting tremor was 2.6 times greater in the ODT group versus the STN DBS & ODT group. [6]

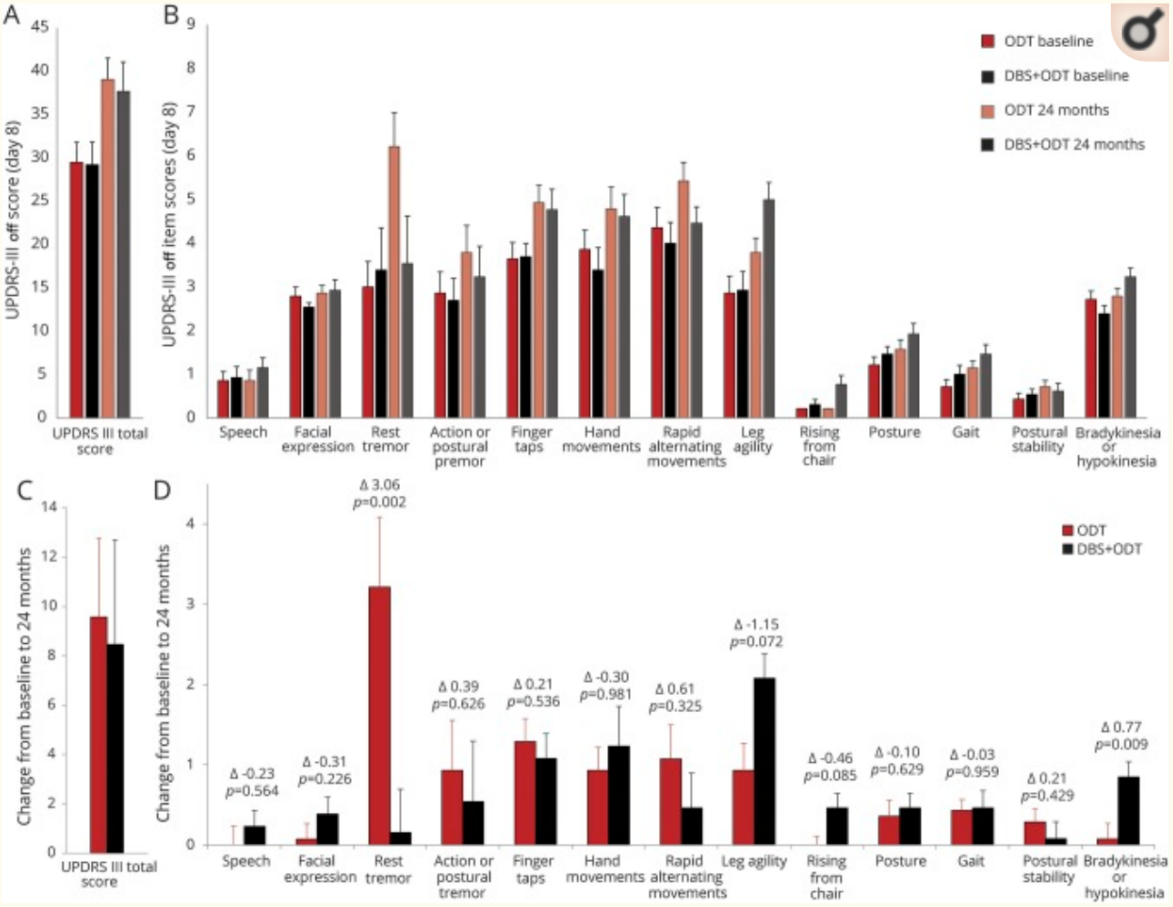

Figure 1

Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) motor examination "off" item scores

Mean ± SEM UPDRS-III scores after a 7-day washout (day 8) by treatment group (n = 14, optimal drug therapy [ODT]; n = 13, deep brain stimulation [DBS] + ODT) and mean ± SEM changes in scores from baseline to 24 months. (A) UPDRS-III total score (excludes rigidity) at baseline and 24 months. (B) UPDRS-III item scores at baseline and 24 months. (C) Change in UPDRS-III total score (excludes rigidity) from baseline to 24 months. (D) Change in UPDRS-III item scores from baseline to 24 months. Δ = ODT minus DBS + ODT difference in change from baseline to 24 months; *p* values determined from Wilcoxon rank-sum test; **p* < 0.0038 (0.05/13) was considered significant for this analysis.

Figure 2. Motor outcomes of "off" therapy.[6]

Overall, the most statistical significance difference between the ODT and the DBS & ODT group was the resting tremor section of the UPDRS-III analysis. In Figure 2 above, there also shows an increase in the ODT group after 24 months in these UPDRS-III categories: action and postural tremor, finger taps, hand movements, and rapid alternating movements. The DBS & ODT group had an increase in score in the UPDRS-III categories: leg agility, rising from a chair,

posture, gait, speech, and bradykinesia or hypokinesia. Both groups had approximately the same scores in facial expression and postural instability.[6]

This study also assessed the mean number of limbs affected by the resting tremor for each patient. At baseline there were 1.4± 0.8 in the ODT group and 1.6± 1.3 in the DBS & ODT group. At the end of the two year study the ODT group had 2.8± 1.3 and the DBS & ODT group had 1.5± 1.3. Overall, the change favored the DBS & ODT group. A total of 86% of patients in the ODT group experienced a new resting tremor in a new limb while the DBS & ODT group only increased by 46%. Four patients in the DBS & ODT group had a resting tremor at baseline that went away by the end of the trial. In one patient in the DBS & ODT group, all tremors completely vanished.[6]

The "on" therapy tremor was also analyzed in both groups. The DBS & ODT group was worse than the ODT group by 1.3 points at baseline. This was not found to be statistically significant (p= 0.18) because of the small sample size represented. The DBS & ODT group did improve by 1.5 points over the 24 month trial for the resting tremor while "on" therapy. Whereas the ODT group worsened by 0.9 points giving the DBS & ODT group the favorable outcome.[6]

When comparing both groups, the DBS & ODT group took less levodopa. The amount of stimulation in the DBS & ODT group did have to be increased throughout the two year period from 1.6 +/- 2V to 1.9 +/- 3 V.[6]

Study Critique:

A limitation of this study is that the research only spanned a course of two years, which does not allow for observation of long-term effects of DBS that may appear for patients receiving it at earlier stages of PD. Another limitation of the study is that UPDRS-III is supposed to include rigidity but, because the patients were videotaped, the rigidity could not properly be assessed. Additionally, the UPDRS-III scoring is a subjective measure without a studied biomarker, so grader error could be present. The participants in the study were also potentially at risk for bias because it was an open-label pilot study.

Strengths of the study include that the neurologist looking at the videos was blinded to which treatment each patient was receiving. The study was also randomized, which increases confidence in the results. Even though the results are favorable and statistically significant in this pilot study, the cohort size will need to be larger before approval of DBS in early PD can be FDA approved.[6]

Study #2

Neurostimulation for Parkinson's Disease with Early Motor Complications (2013)

Study Objective: To assess whether subthalamic deep brain stimulation would benefit patients with earlier staged PD[8]

Study Design:

This was a two year randomized, parallel-group study that took place in Germany and France that aimed to compare DBS with medical therapy versus medical therapy alone. The University of Marburg in Marburg, Germany was selected as the coordinating center that conducted the randomization process that included randomly permuted block lengths for each center. The Declaration of Helsinki, Good Clinical Practice guidelines, and the International Organization for Standardization 14:155 of 2003 were used as standards that the study complied

to and an ethics committee at each center approved the study. All participants signed a written informed consent document prior to the randomization process. Once the study began, a separate committee for data and safety monitored continuously throughout the study. Monitors were used to verify the data at each respective site- German centers at Koordinierungszentrum für Klinische Studien and French centers at Department of Clinical Research, Assistance Publique- Hôpitaux de Paris. The study was designed by the protocol committee and written by the steering committee.[8]

A total of 251 participants out of 392 potential candidates were chosen to be randomly assigned to a study arm of either stimulation plus pharmacotherapy or only pharmacotherapy between July 2006 and November 2009. There were nine German and eight French university centers. The participants needed a PD diagnosis with early motor complications in which the mean age was 52 years, and the mean length of the disease was 7.5 years.[8] The inclusion and exclusion requirements for the selection of these participants can be seen in Table 1. A total of 124 participants were randomized to the deep brain stimulation study arm with 120 finishing the study. A total of 127 participants were assigned to the pharmacotherapy only study arm with 123 finishing the study. The authors noted that after randomization, the baseline demographics and information were similar amongst the two study arms with an average duration of disease being 7.5 years and pharmacotherapy adverse events started 1.7 years prior to enrolling in this study.[8]

Table 1. Inclusion and exclusion criteria for selection of participants[8]

Inclusion:
18-60 years old
Duration of disease 4+ years
Hoehn and Yahr scale below stage 3
Unified Parkinson's Disease Rating Scale- part III showing 50%+ improvement of motor symptoms with use of dopaminergic medication
Fluctuations or dyskinesias for ≤3 years
Unified Parkinson's Disease Rating Scale- part II showing a score of >6 for activities of daily living in the worst condition despite medical treatment
Social and Occupational Functioning Assessment Scale score of 51-81% indicating mild-to moderate impairment of social and occupational functioning
Exclusion:
Mattis Dementia Rating Scale score of ≤130

Beck Depression Inventory II score of >25
Acute psychosis
Any other medical or psychological problem that would interfere with the conduction of the study protocol
Duration of disease <4 years

Within 6 weeks of randomization, the participants that were chosen for the stimulation with pharmacotherapy arm had a stereotactic surgery that included placement of electrodes (model 3389, Medtronic) in the STN and placement of a pulse generator (Kinetra or Soletra, Medtronic). Protocols for surgical standards were followed to assure appropriate anesthesia, imaging pre- and post-implantation, and microelectrode recording. DBS was provided to these participants.[8]

The participants underwent assessments at baseline, 5, 12, and 24 months with a levodopa challenge addition at baseline and 24 months. A video was taken prior to surgery and after surgery at baseline and 24 months so that blinded assessments could have a comparison. Each motor condition was recorded, and two blinded experts assessed the participants' UPDRS-III score from the videos with the exception of rigidity, which was assessed in person. European Federation of Neurological Societies guidelines were used to guide medication and stimulation adjustments to standardize the sequence of changes to therapy, which a separate expert panel evaluated for compliance to the guidelines.[8]

Two suicides occurred during the study, prompting an additional procedure in the protocol that assessed a baseline risk of suicidality and a phone interview every two months. Psychiatric help was available when needed.[8]

The primary outcome measured included the Parkinson's Disease Questionnaire (PDQ-39) mean change in quality of life at baseline and two years between the two study arms. Using a serial gatekeeper procedure, if the results were significant, the study assessed other outcomes including motor symptoms via UPDRS-II activities of daily living, UPDRS-III severity of motor signs, UPDRS-IV severity of treatment complications, and patient reported "good" mobility and no dyskinesias that interfered with activities. Other minor secondary outcomes were assessed but were not relevant to the purposes of this literature review. Any adverse events were recorded throughout the study.[8]

Statistical analysis included an assumption of normally distributed data and therefore a power of 80% was chosen for a two-sided Mann-Whitney test. The number of necessary participants were calculated to be 246 using a standardized effect size of 0.4 with alpha=5% and an estimated loss to follow-up of 15%. The authors noted that intention-to-treat analysis was utilized first and that per-protocol analysis was also conducted separately. Instead of the Mann-Whitney test, a linear mixed-model analysis was used to allow for adjustments and accountability of random effects. Loss to follow-up that resulted in lack of data points were managed using direct likelihood analysis. The outcomes were evaluated using Hochberg's multiple-comparison method using a 5% significance level.[8]

A total of 25 participants deviated from the study protocol by completing the PDQ-39 after the completion date, having an absence of motor fluctuations or dyskinesias, lacking the entirety of the treatment, or dying during the study. This left 116 participants in the stimulation study arm and 110 in the pharmacotherapy study arm for result analysis.[8]

Study Results:

PDQ-39 score measured as the primary outcome showed an enhancement of 26% in the stimulation study arm, and a decline of 1% in the pharmacotherapy study arm between the baseline assessment and 24 months. The between-group difference was an 8.0 point change ($p=0.002$) on the score.[8]

Pharmacotherapy was withheld for at least 12 hours for the off-medication circumstances in the stimulation study arm. A 53% improvement in the UPDRS-III scores were seen in the stimulation study arm with the between-group difference at the conclusion of the study 16.4 points better in this group ($p<0.001$). There was noted to be no change in the pharmacotherapy group ($p<0.001$). A lesser, but still statistically significant improvement in UPDRS-III scores were observed between the stimulation arm when on-medication and on-stimulation. Levodopa adverse events such as motor fluctuations and dyskinesias were evaluated using UPDRS-IV scores and showed 61% amelioration in those with stimulation and a 4.1 point change was noted between groups ($p<0.001$).[8]

UPDRS-II activities of daily living scores at the worst point in the prior week changed by 6.2 points showing stimulation was superior to medication only ($p<0.001$) without differences between groups for the best point in the week. The patient reported mobility and lack of dyskinesia was 20% better in the stimulation group and a between-group improvement of 1.9 hours ($p=0.01$). Poor mobility was decreased by 1.8 hours ($p=0.006$) for the stimulation group. There was no significance noted in time with debilitating dyskinesia between groups.[8]

The levodopa medication doses decreased by 39% in the stimulation group and increased by 21% in the pharmacotherapy participants for a total between-group difference of 609 mg ($p<0.001$). Other endpoints were measured by this study; however, are not the focus of this literature review.[8]

Table 2. Study outcomes[8]

Table 2. Primary, Major, and Minor Secondary End Points.*

End Point	Baseline				Within-Treatment Change from Baseline to 24 Months				Between-Group Difference in Change from Baseline (95% CI)	P Value
	Neurostimulation		Medical Therapy		Neurostimulation		Medical Therapy			
	no. of patients	*mean ±SE*	*no. of patients*	*mean ±SE*	*mean ±SE*	*% change from baseline*	*mean ±SE*	*% change from baseline*	*mean ±SE*	
Primary end point										
PDQ-39 summary index score, intention-to-treat population	124	30.2±1.3	127	30.2±1.3	7.8±1.2	26†	−0.2±1.1	−1	8.0±1.6 (4.2 to 11.9)	0.002
PDQ-39 summary index score, per-protocol population	110	30.1±1.4	116	30.1±1.3	8.1±1.2	27†	0.0±1.2	0	8.1±1.7 (2.8 to 13.4)	0.02
Major secondary end points										
UPDRS-III score, without medication	123	33.2±1.8	127	33.0±1.8	17.5±1.0	53†	1.2±1.0	4	16.4±1.4 (13.7 to 19.1)	<0.001‡
UPDRS-II score during worst condition	123	15.0±0.8	126	14.8±0.8	4.5±0.6	30†	−1.7±0.6	−12†	6.2±0.9 (4.5 to 8.0)	<0.001‡
UPDRS-IV score	123	5.6±0.3	127	5.5±0.3	3.4±0.3	61†	−0.7±0.3	−13†	4.1±0.4 (3.2 to 4.9)	<0.001‡
Time with good mobility and no troublesome dyskinesia (hr)§	105	10.3±0.5	110	10.3±0.5	2.1±0.5	20†	0.2±0.5	2	1.9±0.8 (0.4 to 3.4)	0.01‡
Minor secondary end points										
SCOPA-PS score	124	9.1±0.5	126	9.0±0.5	2.5±0.5	28†	0.4±0.5	3	2.1±0.7 (0.4 to 3.9)	0.02
Motor outcomes										
UPDRS-III score, without medication and without assessment of rigidity, on blinded review	111	25.4±1.1	114	25.1±1.1	9.6±0.8	38†	1.0±0.8	4	8.6±1.1 (6.4 to 10.9)	<0.001
UPDRS-III score, with medication and stimulation	122	12.5±1.5	127	12.1±1.5	3.2±0.7	26†	−1.3±0.6	−11†	4.5±0.9 (2.7 to 6.4)	<0.001
UPDRS-II score during best condition	123	4.9±0.6	126	4.9±0.6	−0.1±0.5	−2	−0.6±0.4	−12	0.5±0.6 (−0.8 to 1.7)	0.49
Levodopa-equivalent daily dose (mg)	124	935.6±21.5	127	950.3±21.3	−363.3±19.4	−39†	245.8±18.8	21†	−609.1±27.0 (−662.1 to −556.1)	<0.001
Cognitive and affective outcomes										
UPDRS-I score	123	1.1±0.2	127	1.1±0.2	−0.2±0.2	−9	−0.5±0.2	−36†	0.3±0.2 (−0.2 to 0.8)	0.22
Mattis Dementia Rating Scale score	124	140.3±0.4	127	140.4±0.4	−1.3±0.4	−1†	−0.6±0.4	−0.4	0.7±0.6 (−0.6 to 1.9)	0.28
Brief Psychiatric Rating Scale score	124	25.3±1.0	127	25.2±1.0	1.9±0.7	7†	−0.3±0.7	−1	2.2±1.0 (0.2 to 4.1)	0.03
Montgomery and Åsberg Depression Rating Scale score	123	6.7±0.8	127	6.6±0.8	1.1±0.6	16	−1.3±0.6	−20†	2.4±0.8 (0.8 to 4.0)	0.004
Beck Depression Inventory II score	124	10.1±0.6	127	10.1±0.6	1.8±0.6	18†	−0.1±0.6	−2	1.9±0.8 (0.3 to 3.6)	0.02
Starkstein Apathy Scale score	124	9.9±0.7	127	9.8±0.7	−2.8±0.5	−28†	−1.6±0.5	−16†	−1.2±0.7 (−2.4 to 0.1)	0.08

* Scores on the Parkinson's Disease Questionnaire (PDQ-39) summary index range from 0 to 100, with lower scores indicating better quality of life. Scores on the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III), for the assessment of motor function, range from 0 to 108, with higher scores indicating worse functioning; patients in the neurostimulation group were assessed with stimulation. Scores on the UPDRS-II, for the assessment of activities of daily living, range from 0 to 52, with higher scores indicating worse functioning. Scores on the UPDRS-IV, for the assessment of levodopa-induced complications, range from 0 to 23, with higher scores indicating worse functioning. Scores on the Scales for Outcomes in Parkinson's Disease–Psychosocial (SCOPA-PS) questionnaire range from 0 to 33, with higher scores indicating worse functioning. Scores on the UPDRS-I, for the assessment of emotion and cognition, range from 0 to 16, with higher scores indicating worse functioning. Scores on the Mattis Dementia Rating Scale range from 0 to 144, with higher scores indicating better functioning. Scores on the Brief Psychiatric Rating Scale range from 18 to 126, with higher scores indicating worse functioning. Scores on the Montgomery and Åsberg Depression Rating Scale range from 0 to 60, with higher scores indicating worse functioning. Scores on the Beck Depression Inventory II range from 0 to 63, with higher scores indicating worse functioning. Scores on the Starkstein Apathy Scale range from 0 to 42, with higher scores indicating worse functioning. Positive values for changes over time for the within-group and between-group comparisons indicate improvement in functioning or quality of life, except for changes in the levodopa-equivalent daily dose. Mixed-model analyses were performed for each end point assuming normally distributed data, with the baseline value for baseline adjustment, main effects for group and time, a group-by-time interaction term, study center as a random effect, and a generalized covariance matrix to account for serial dependency among observations. Reported are the generalized least-squares estimates with standard errors.

† P<0.05 for the within-group change.

‡ P values for the major secondary end points were calculated after adjustment for multiple comparisons with the use of Hochberg's method.[32]

§ Data are based on entries in patient diaries of motor function, recorded every 30 minutes over a 24-hour period on 3 consecutive days. The diary results for a day were included in the analysis if valid entries were made concerning at least 42 of the 30-minute periods per day (21 hours per day).

Adverse events were reported in both groups to be similar- 68 in the stimulation group and 56 in the pharmacotherapy group had a minimum of one adverse event. Three suicide events occurred, two being in the stimulation group and the other in the pharmacotherapy group. No other deaths occurred. Side effects of suicidal ideation and suicide attempts were relatively the same between study arms. The stimulation group did show more depression symptoms. Motor control, impulse control, and psychotic events had a higher frequency in the pharmacotherapy group. Only one of 26 complications related to the brain stimulation surgery caused permanent damage, which resulted in a scar.[8]

Overall, 96.8% of the stimulation study arm participants and 94.5% of the pharmacotherapy study arm participants complied with medical therapy guidelines. The mean parameters after 24 months were 2.8±0.7V stimulation strength, 142±27 Hz for frequency, and 66±33 µs for pulse duration.[8]

Study Critique:

A limitation of this study is that it only spanned the course of 24 months, which does not allow for observation of long-term effects of DBS that may appear for those receiving it at earlier stages of PD. Assessment of the overall safety of this therapy type cannot be determined from this study because of its short course.

The study implemented strong and rigorous protocols with exceptional oversight and medical care for any adverse events that occurred. The sample size was larger and appropriately maintained. The randomization and blinded format of the study are also strengths of this study. The intention-to-treat and per-protocol results were very similar indicating confidence in the validity of the results.

Study #3

Acute Effects of Subthalamic Deep Brain Stimulation on Motor Outcomes in Parkinson's Disease; 13 Year Follow Up (2019)

Study Objective: To assess the efficacy of STN DBS on motor symptoms of Parkinson's over 10 years.[9]

Study Design:

This was a prospective cohort study registered in the Clinical Trial Registry with protocol approval from the Ruijin Hospital Ethics Committee of Shanghai Jiao Tong University School of Medicine in Shanghai, China. Nine men and two women were chosen to be study participants for a total of 11 patients. The study participants had a diagnosis of early-onset PD and were recruited from patients of the Departments of Neurology and Functional Neurosurgery at Ruijin Hospital, Shanghai Jiao Tong University School of Medicine in Shanghai, China. Inclusion criteria were defined as the following: idiopathic PD defined by the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria, utility of bilateral STN-DBS implant for greater than 10 years, PD diagnosis prior to the age of 50, and length of disease time seven years or less when surgery occurred. Exclusion criteria included unstable vital signs or other medical and/or psychiatric comorbidities during the conduction of the study. All patients signed a written informed consent prior to participating. Those that were selected were between the ages of 43 and 68 years old with a mean onset of PD being 38.9±7.5 years and the mean age when surgery was completed being 43.8±8.7 years. At the onset of the study, the continuous STN-DBS treatment the participants had already received averaged 13.4±1.3 years.[9]

Neurosurgery was conducted by targeting specific locations determined using 1.5T magnetic resonance imaging (MRI). Model 3387-40, 7428 electrodes manufactured by Medtronics in Minneapolis, MN were embedded into the subthalamic nucleus while the patient was under local anesthesia. During the procedure, macroelectrode stimulation was utilized to assure the appropriate position of the implanted electrodes. The programmable pulse generator (IPG) (bilateral Itrel II®, unilateral Kinetra) manufactured by Medtronic, and the deep brain stimulation leads and extension wires (7482) manufactured by Medtronic were placed under the clavicle using general anesthesia. The IPG was configured the next day and the electrical parameters were adjusted via the DBS programmer (7532, 8840 neurological programmer) manufactured by Medtronic and included parameters such as voltage, pulse width, and frequency. Imaging was used after surgery to assure DBS leads were in the appropriate location. A non-rechargeable Medtronic pulse generator (model 7428 Kinetra, or 7426 Soletra™) was

used to distribute the stimulation. Batteries necessitated replacement 3.9±1.3 times as the average lifespan of the battery was 4.1±1.3 years. During the final battery replacement, a Medtronic Activa™ pulse generator (model 37602 or 37612) was provided.[9]

Primary outcomes were severity of motor symptoms (tremor, rigidity, and bradykinesia) as defined by UPDRS-III, gait and freezing of gait as defined by the Timed Up and Go (TUG) test, and the disability extent and progression as defined by the Hoehn-Yahr stage.[9]

The stimulation details were noted at every visit in addition to at the time of any adverse events. A formula was used to calculate the total electrical energy delivered in one second ($TEED_{1s}$) at the conclusion visit. Assessments were conducted at various times. The off-medication assessment was conducted after dopaminergic drugs were discontinued the night prior. The on-medication assessment was obtained 45 minutes after the participant had taken their antiparkinsonian medications with the brain stimulator on. One final assessment was taken with the brain stimulator turned off an hour later. During visits, motor assessments were videoed so that an examiner who was blinded to patient information and STN-DBS parameters could score the patient's symptoms.[9]

Statistical analysis was performed between stimulation on and off assessments and at different visits using non-parametric Wilcoxon signed-ranks tests using Statistical Package for Social Sciences for Windows. Statistically significant data were defined as two-sided $p<0.05$ and adjustments for multiple testing were made using the False Discovery Rate (FDR) correction.[9]

Study Results:

The study showed a statistically significant improvement in the total UPDRS-III score outcome. Specifically, there was a 54% reduction in motor symptoms in the off-medication/on-stimulation versus the on-medication/off-stimulation and a 48% reduction in motor symptoms in the on-medication/on-stimulation versus on-medication/off-stimulation. Tremor was controlled significantly showing a 72% reduction off-medication and a 69% reduction on-medication. Bradykinesia was reduced 45% off-medication and 40% on-medication. The summation of total axial symptoms were reduced 51% off-medication and 44% on medication. However, dissecting axial symptoms further gait was more responsive to the stimulation and showed a 56% reduction off-medication and 50% reduction on-medication, while posture was only reduced 38% on-medication and 27% off-medication. The TUG scores indicate an improvement of functional mobility with a 70% reduction of scores off-medication and a 47% reduction in scores on-medication. A 54% reduction in time percentage spent in FOG was seen off-medication and a 58% reduction was seen on-medication.[9]

Table 3. Motor symptom severity of patients (N=11) before and after STN-DBS.[9]

Table 1

Motor symptom severity of patients ($N = 11$) before and after STN-DBS*.

	Med off		Med on		*P*-value	
	Stim off	**Stim on**	**Stim off**	**Stim on**	**Med off**	**Med on**
UPDRS III						
Total	58.2 ± 19.9	26.8 ± 14.1	51.1 ± 22.7	26.8 ± 14.1	0.003	0.003
Tremor *(item 20, 21)*	3.9 ± 3.7	1.1 ± 2.1	2.9 ± 3.4	0.9 ± 1.9	0.018	0.018
Rigidity *(item 22)*	12.6 ± 5.1	3.6 ± 3.3	10.4 ± 6.2	3.5 ± 3.4	0.003	0.005
Bradykinesia *(item 19, 23–26,31)*	31.1 ± 9.0	17.0 ± 8.8	28.3 ± 9.6	17.0 ± 8.8	0.003	0.005
Axial symptoms *(item 18, 27–30)*	10.6 ± 5.0	5.2 ± 2.5	9.3 ± 5.4	5.2 ± 2.5	0.003	0.008
Gait *(item 29)*	2.5 ± 1.3	1.1 ± 0.9	2.2 ± 1.4	1.1 ± 0.9	0.003	0.01
Posture *(item 28)*	1.3 ± 0.7	0.8 ± 0.8	1.1 ± 0.5	0.8 ± 0.8	0.102	0.083
Timed up and go N^a						
Total time in seconds	33 ± 48	10 ± 4	18.6 ± 14.3	9.9 ± 3.7	0.017	0.017
Time percentage spend in FOG, %	27.3 ± 29.8	12.6 ± 15.7	27.3 ± 29.8	11.4 ± 13.3	0.018	0.018
Hoehn-Yahr stage	3.3 ± 1.0	2.5 ± 0.6	3.2 ± 1.0	2.5 ± 0.6	0.007	0.017

**Data represent mean and standard deviation. The two stimulation conditions differed significantly from each other at p <0.05 for all variables in both medication-on and -off state, except Posture (item 28), as assessed by two-tailed Wilcoxon signed-ranks tests. Significance-levels were adjusted using False Discovery Rate (FDR) Correction to account for multiple testing.*

STN, subthalamic nucleus; DBS, deep brain stimulation; UPDRS, United Parkinson Disease Rating Scale.

N^a = 7, 4 of 11 patients can walk only with stimulation in both medication -on and -off state.

After the conclusion of the final assessment, the study noted that dopaminergic medication dosages were reduced by 53%. At baseline, the levodopa daily dose was 750±224mg, while 13 years post-surgery the daily dose was 356±397mg. The study did mention that two participants discontinued dopaminergic medication because of hallucinations as a side effect of the medication and had adequate motor control. Another two participants needed less than 100mg/day of levodopa to decrease the amount of dyskinesia experienced as a side effect of the medication.[9]

Pertinent stimulation parameters mentioned that monopolar stimulation with single or double unipolar configuration was used in 90% of the cohort. The voltage needed increased over

the course of the study; however, the frequency of stimulation was decreased. The pulse width stayed consistent during stimulation after the first visit. The reported total electrical energy delivered was noted to be 343.6±118.8μW.[9]

Table 4. Stimulation parameters at follow up visits after surgery[9]

Table 2

Stimulation parameters at follow up visits 1 month, 1 year, 5 years, 8 years, and 13 years after surgery*.

Stimulation parameters	1 month	1 year	5 year	8 year	13 year
Amplitude (V)	2.15 ± 0.16	2.51 ± 0.25[a]	2.84 ± 0.40[a,b]	3.00 ± 0.42[a,b,c]	3.11 ± 0.34[a,b,c]
Pulse width (μs)	60 ± 0	74 ± 16[a]	82 ± 24[a]	82 ± 24[a]	92 ± 18[a,b]
Rate (Hz)	165 ± 10	163 ± 12	152 ± 10[a,b]	140 ± 18[a,b, c]	128 ± 26[a,b,c]

*Data represent mean and standard deviation.
[a]p significant compared with 1 month after surgery.
[b]p significant compared with 1 year after surgery.
[c]p significant compared with 5 years after surgery. p <0.05 was considered as significant difference, using two-tailed Wilcoxon signed-ranks tests.

During the first three months of the study, four participants experienced dyskinesia related to the stimulation, which was managed by decreasing the amount of stimulation or medication. During the first year, three patients gained approximately 8 kg. There were no hardware or surgical setbacks noted throughout the study.[9]

The study concluded that there is statistically significant improvement in motor and axial symptoms of early-onset PD that can be sustained. The surgery was without complications and all stimulation side effects were managed adequately by decreasing medication doses or adjusting stimulation parameters. The authors noted that programming should be conducted by experts in order for patients to receive maximum benefit from this therapy.[9]

Study Critique:

One major limitation of this study is that the sample size is extremely small and limited with only 11 participants. In addition, it is not a randomized control study and there were not controls noted; however, controls would be difficult to implement in this type of study as all PD patients manifest differently. The on and off medication circumstances studied in conjunction with stimulation were not in a randomized order causing a lack of a wash-out period that could have caused an alteration in results. The authors admit to the inability to receive baseline UPDRS scores prior to the stimulation treatment. This makes comparing results pre- and post-surgery

difficult when assessing motor symptoms, and should be considered in future long-term research for more accurate analysis. Additionally, the study notes that dyskinesias occurred in a subset of the participants from either the stimulation or the medication, but did not truly indicate which was the cause of the adverse event. This is important in determining the effectiveness and utility of stimulation.[9]

The study assessed various motor symptoms using three different well studied assessment tools such as the UPDRS-III and Hoehn-Yahr stage. This offers useful credibility and ease of understanding results to others experienced with understanding PD management. The longevity of the study is also an asset. The study was conducted over a minimum of 10 years, providing useful long-term data regarding this treatment option, which is not well studied in the population of early-onset PD. The study results were noted to be consistent with previous long-term studies managing axial symptoms; however, there are still conflicting reports noted in other studies. It is evident that close expert management of stimulation parameters and evaluation of symptoms is necessary to effectively incorporate this treatment option.[9]

DISCUSSION

Parkinson's disease is a progressive disease without modifying or curative therapy options. While there are many medication options to treat the symptoms of PD, these therapies do not come without consequences and do not slow the progression of the disease. In addition, over time the dosages must be increased to maintain the therapeutic effects that are desired. This leads to complicated medication regimens, more side effects, and higher cost to the patients. STN DBS offers a solution to these problems, but thus far has only been implemented successfully in refractory cases of PD. The studies selected for this systematic review aim to determine if implementation of this treatment modality would help motor symptoms specifically in earlier stage PD. The pilot studies chosen, indicate promising results in the use of STN DBS in early onset PD on motor symptoms in addition to reducing the dose of the levodopa needed in order to control symptoms.

An overview of the three studies can be viewed in Table 5. Limitations of Hacker et al. and Zhou et al. include extremely small sample sizes.[6,9] Additionally, the Zhou et al. study did not complete a randomized control trial, thus decreasing the strength of the results. However, the participants were followed for 13 years, which is significantly longer than the other two studies and thus provides a better understanding of the long-term effects of this treatment option.[6,8,9] Because the goal was to evaluate the use of this therapy in earlier onset PD, it is important to consider the long-term effects of DBS in this patient population as they will be utilizing this modality for a much longer period of time than someone with advanced PD at the end of their life span. No major or serious side effects were mentioned in this long-term study. Contrary to these findings, Schuepbach et al. had a much better sample size, but reported significant psychological adverse events, including successful suicide attempts within the two year period the participants were followed. The authors were unable to identify and attribute the cause of these events to the STN DBS, but this is a major consideration in considering this treatment for those with early PD. If significant psychological adverse events occur because of STN DBS, this may not be a treatment protocol that is worth the risk despite the positive motor benefits reported.[8]

Hacker et al. focused significantly on the resting tremor. The development of new tremors in previously unaffected limbs were noted to be significantly lower with the STN DBS, a character not addressed in the other studies. In addition, the existing tremors were decreased to a

statistically significant amount as well as the participants reporting that this feature of their treatment was the most favored benefit.[6] Schuepbach et al. showed strength in their sample size and found that UPDRS-III scores decreased to a statistically significant degree ($p<0.001$). Notably, the dyskinesia symptoms often seen with levodopa treatment were reduced significantly in those receiving STN DBS, which was not discussed in other studies.[8] Zhou et al. indicated statistically significant ($p<0.05$) improvement in those with STN DBS in comparison to only medication in all motor symptoms assessed except posture. UPDRS-III scores decreased, indicating improvement of motor symptoms such as tremor, rigidity, and bradykinesia, which are all cardinal motor symptoms in PD. Gait was shown to improve as well as the TUG test. Given that this was the longest of the studies, the improvements of motor function appear to be maintained long-term with the use of the STN DBS from an earlier stage of the disease.[9]

Each study focused on slightly different aspects of the disease manifestations; however, collectively, all three studies showed statistically significant reductions in the tremors the participants experienced, a hallmark symptom of PD.[6,8,9] Further studies involving larger sample sizes and longer duration trials should be done to determine the efficacy and safety of STN DBS in earlier stages of PD. The research from these trials indicates the possibility of this treatment in the future.

Table 5. Overview of Studies[6,8,9]

Study	Hacker et al.	Schuepbach et al.	Zhou et al.
Patients	28	251	11
Age	50-75	18-60	43-68
Place of Study	Vanderbilt University	Marburg, Germany	Shanghai, China
Population	- Hoehn & Yahr score of 2 while "off" medication time - History of taking PD medications for six months to four years	- Duration of disease 4+ years - Hoehn and Yahr scale below stage 3 - Unified Parkinson's Disease Rating Scale- part III showing 50%+ improvement of motor symptoms with use of dopaminergic medication - Fluctuations or dyskinesias for ≤3 years - UPDRS-II showing a score of >6 for activities of daily living in the worst condition despite medical treatment - Social and Occupational Functioning Assessment Scale score of 51-81% indicating mild-to moderate impairment of social and occupational functioning.	- Idiopathic PD defined by the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria - Utility of bilateral STN DBS implant for greater than 10 years - PD diagnosis prior to the age of 50 - Length of disease time seven years or less when surgery occurred
Study type	RCT	RCT	Prospective Cohort
Measurement scale	Hoehn and Yahr UPDRS-III	Hoehn and Yahr UPDRS-III	Hoehn and Yahr UPDRS-III
STN DBS protocol	- Frequency and pulse width was set at 60 μs and 130 Hz using monopolar stimulation	- The mean parameters after 24 months were 2.8±0.7V stimulation strength, 142±27	- Pertinent stimulation parameters mentioned that monopolar stimulation with single or double unipolar

	- The amount of stimulation in the DBS & ODT group did have to be increased throughout the 2 year period from 1.6 +/- 2V to 1.9 +/- 3 V.[6]	Hz for frequency, and 66±33 μs for pulse duration.[8]	configuration was used in 90% of the cohort - The voltage needed increased over the course of the study; however, the frequency of stimulation was decreased. - The pulse width stayed consistent during stimulation after the first visit. The reported total electrical energy delivered was noted to be 343.6±118.8μW.[9]
Length of Study	2 years	2 years	13 years

CONCLUSION

STN DBS is shown to improve motor symptoms in early PD such as an overall improvement in the patient's UPDRS-III scores and the ability to reduce the amount of levodopa taken. Even though most of the results were statistically significant, due to the small cohorts in two of the three studies and span of two of the three studies being only two years, some of the concerns stem from the long-term impact of STN DBS. The variability among the STN DBS protocol parameters is also a concern among these studies. Additionally, there is a limitation on experts in DBS protocols given the specificity of the protocols and continuous monitoring and adjustments made throughout therapy that will restrict the implementation of this treatment as standard practice. Furthermore, insurance coverage and cost of this procedure in comparison to medications would be a concern for PD patients. While STN DBS shows promising improvements in PD motor symptoms, the choice to undergo this treatment must be an individual conversation for each patient and their provider with a risk versus benefit analysis on a case-by-case basis.

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