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ORIGINAL ARTICLE

Pallidal versus Subthalamic Deep-Brain Stimulation for Parkinson's Disease

Kenneth A. Follett, M.D., Ph.D., Frances M. Weaver, Ph.D., Matthew Stern, M.D., Kwan Hur, Ph.D., Crystal L. Harris, Pharm.D., Ping Luo, Ph.D., William J. Marks, Jr., M.D., Johannes Rothlind, Ph.D., Oren Sagher, M.D., Claudia Moy, Ph.D., Rajesh Pahwa, M.D., Kim Burchiel, M.D., Penelope Hogarth, M.D., Eugene C. Lai, M.D., Ph.D., John E. Duda, M.D., Kathryn Holloway, M.D., Ali Samii, M.D., Stacy Horn, D.O., Jeff M. Bronstein, M.D., Ph.D., Gatana Stoner, R.N., C.C.R.C., Philip A. Starr, M.D., Ph.D., Richard Simpson, M.D., Ph.D., Gordon Baltuch, M.D., Ph.D., Antonio De Salles, M.D., Ph.D., Grant D. Huang, Ph.D., and Domenic J. Reda, Ph.D., for the CSP 468 Study Group*

ABSTRACT

BACKGROUND

Deep-brain stimulation is the surgical procedure of choice for patients with advanced Parkinson's disease. The globus pallidus interna and the subthalamic nucleus are accepted targets for this procedure. We compared 24-month outcomes for patients who had undergone bilateral stimulation of the globus pallidus interna (pallidal stimulation) or subthalamic nucleus (subthalamic stimulation).

METHODS

At seven Veterans Affairs and six university hospitals, we randomly assigned 299 patients with idiopathic Parkinson's disease to undergo either pallidal stimulation (152 patients) or subthalamic stimulation (147 patients). The primary outcome was the change in motor function, as blindly assessed on the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III), while patients were receiving stimulation but not receiving antiparkinsonian medication. Secondary outcomes included self-reported function, quality of life, neurocognitive function, and adverse events.

RESULTS

Mean changes in the primary outcome did not differ significantly between the two study groups (P=0.50). There was also no significant difference in self-reported function. Patients undergoing subthalamic stimulation required a lower dose of dopaminergic agents than did those undergoing pallidal stimulation (P=0.02). One component of processing speed (visuomotor) declined more after subthalamic stimulation than after pallidal stimulation (P=0.03). The level of depression worsened after subthalamic stimulation and improved after pallidal stimulation (P=0.02). Serious adverse events occurred in 51% of patients undergoing pallidal stimulation and in 56% of those undergoing subthalamic stimulation, with no significant between-group differences at 24 months.

CONCLUSIONS

Patients with Parkinson's disease had similar improvement in motor function after either pallidal or subthalamic stimulation. Nonmotor factors may reasonably be included in the selection of surgical target for deep-brain stimulation. (ClinicalTrials.gov numbers, NCT00056563 and NCT01076452.)

*The affiliations of authors are listed in the Appendix. A complete list of members of the Veterans Affairs Cooperative Studies Program (CSP) 468 study group is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. Address reprint requests to Dr. Weaver at the Hines Veterans Affairs Hospital Center for Management of Complex Chronic Care, 5000 S. 5th Ave., 151H, Hines, IL 60141, or at frances.weaver@va.gov.

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Randomized studies have shown that treatment with deep-brain stimulation, which involves the surgical implantation of a device that sends electrical impulses to specific parts of the brain, is superior to medical therapy for improving motor function and quality of life for patients with advanced Parkinson's disease.[1,2] The globus pallidus interna and the subthalamic nucleus are both accepted targets for deep-brain stimulation. The subthalamic nucleus is used more commonly as the target, despite the lack of evidence showing that neurostimulation of this target provides a better outcome. Our multicenter, randomized, blinded trial, called the Veterans Affairs Cooperative Studies Program (CSP) 468 study, was designed to compare the outcome of bilateral neurostimulation of the globus pallidus interna (pallidal stimulation) with that of the subthalamic nucleus (subthalamic stimulation).

Methods

Study Design

The details regarding study-site selection, the recruitment and assessment of patients, surgical interventions, and follow-up have been described previously.[1] In brief, 316 patients were enrolled at seven Veterans Affairs and six affiliated university medical centers. Patients with idiopathic Parkinson's disease who were at least 21 years of age were eligible if they had disease that was assessed as stage 2 or higher on the basis of the Hoehn and Yahr disability scale (on which scores range from 0 to 5, with higher scores indicating greater disability) while not receiving antiparkinsonian medication,[3] had a response to levodopa, had persistent and disabling symptoms (e.g., motor fluctuations and dyskinesia) despite optimal medical therapy, had at least 3 hours per 24-hour period with poor motor function or symptom control, and had been receiving medical therapy with no changes in the regimen for at least 1 month.

The first 255 patients participated in a 6-month comparison of medical therapy and deep-brain stimulation in which patients were randomly assigned to receive medical therapy or to undergo deep-brain stimulation (randomized to either pallidal or subthalamic stimulation). After completing 6 months of medical therapy, patients proceeded to deep-brain stimulation, with random assignment to either pallidal or subthalamic stimulation. An interim analysis indicated that a sample of 255 patients was sufficient for the comparison between medical therapy and deep-brain stimulation, so the remaining 61 patients were randomly assigned directly to undergo pallidal or subthalamic stimulation.

Strict adherence to inclusion and exclusion criteria was maintained throughout the study. All patients who were assigned to undergo pallidal or subthalamic stimulation were followed for 24 months after surgery. Randomization was stratified according to study site and the patient's age (<70 vs. ≥70 years). Patients underwent surgery within 1 month after randomization and remained unaware of the surgical target for the duration of the study.

Evaluation

We evaluated patients after a 12-hour overnight withdrawal of antiparkinsonian medication. The stimulator was then turned off, and the patient was evaluated 60 minutes later ("without medication and without stimulation"). Finally, the stimulator was turned back on, and the patient took the usual dose of medication and was evaluated after 60 minutes ("with medication and with stimulation").

At baseline, we evaluated motor symptoms in the absence of medication (in the "practically defined off state"),[4] using part III (motor subscale) of the Unified Parkinson's Disease Rating Scale (UPDRS-III, on which scores range from 0 to 108 and higher scores indicate more severe motor symptoms)[5] and the "stand–walk–sit" test.[4] (All ranges of scores are listed in Table 1.) These evaluations were performed by study-site personnel and independently by movement-disorders clinicians who were unaware of study-group assignments.

We also assessed the patients' performance with medication, using the UPDRS-III,[4] the Hoehn and Yahr scale of disability,[3] the Schwab and England scale of activities of daily living,[6] the stand–walk–sit test[4]; subscales of the UPDRS, including part I (mentation, behavior, and mood), part II (activities of daily living), and part IV (complications of therapy)[5]; the Parkinson's Disease Questionnaire–39 Items (PDQ-39)[7]; and the Beck Depression Inventory II. The study nurse recorded medications that the patients were taking and assessed their physical health status and symptoms of Parkinson's disease. A neuropsychologist administered a battery of neurocognitive tests.

Motor function was also assessed on the basis of diaries that the patients kept.[8] They were

trained in the use of the diaries[9] and completed practice entries. Patients recorded which of four categories (good motor function, motor function with dyskinesia that interfered with movement, poor motor function, or asleep) best reflected the condition of their predominant functioning for the previous 30 minutes in half-hour intervals for 2 days.[8] The time spent in each category was averaged during the 2-day period.

FOLLOW-UP

Patients returned to the study site at 3, 6, 12, 18, and 24 months. The entire baseline assessment, including an evaluation of motor function performed in a blinded fashion, was repeated at 6 and 24 months. Abbreviated assessments were conducted at 3, 12, and 18 months. Study neurologists directed postoperative treatment to achieve optimal control of symptoms without regard to the target of deep-brain stimulation. Management included adjustment of pharmacologic therapy (dose and regimen of dopaminergic and nondopaminergic medications) and nonpharmacologic treatments (e.g., physical, occupational, and speech therapy).

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was the change in the UPDRS-III motor score from baseline to 24 months among patients who were receiving stimulation without medication, as determined by evaluators who were unaware of study-group assignments. Secondary outcomes included self-reported function, quality of life, neurocognitive function, and adverse events.

ADVERSE EVENTS

Patients were queried about adverse events by the study nurse, and such events were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 11.0, and categorized as mild, moderate, or severe in intensity. Adverse events related to Parkinson's disease were queried with the use of a script. All other adverse events were identified by the study nurse during an interview regarding the patients' medical history since the previous follow-up visit. Serious adverse events included any event that resulted in death, disability, or prolonged or new hospitalization or that was life-threatening or required medical or surgical intervention.

STUDY OVERSIGHT

The Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development and the National Institute of Neurological Disorders and Stroke provided financial support for this study and contributed to the study design. Medtronic provided financial support. The stimulators were purchased from the manufacturer, which had no role in the study design, data accrual, data analysis, or manuscript preparation.

The authors were responsible for the collection, management, and analysis of the data and for the preparation of the manuscript and the decision to submit it for publication.

STATISTICAL ANALYSIS

All analyses were based on the intention-to-treat principle. For patients with at least one follow-up visit but incomplete data, the last observation was treated as the 24-month observation. Patients for whom any baseline data or data from follow-up at both 3 and 6 months were missing were deemed to have no change in score. For patients who were initially assigned to receive medical therapy only, the 6-month evaluation, performed just before they underwent deep-brain stimulation surgery, was considered to be the baseline for our analyses. Otherwise, the 3-month or baseline evaluation of medical therapy was treated as the baseline observation for patients undergoing deep-brain stimulation.

We compared the primary outcome in the two study groups using a two-sample t-test. Analysis of mixed-effects models of UPDRS-III motor scores was performed on the assumption that data were missing at random. The time of evaluation was treated as a categorical variable. Differences between study groups were compared by hypothesis tests. Secondary outcomes were measured as changes from baseline to 24 months. Medication use was converted to levodopa equivalents for analysis.[10]

The study was designed to detect a between-group difference of 25% in the primary outcome (the change in the UPDRS-III score at 24 months) with a power of 80%, assuming a correlation of more than 0.25 between UPDRS-III motor scores before and after the intervention (or a difference of 20% with a power of 90%, assuming a correlation of more than 0.50), at an alpha level of 0.05.

Table 1. Characteristics of the Patients at Baseline, According to Study Group and Order of Trial Entry.*

Characteristic	Study Group			Order of Trial Entry			
	Pallidal Stimulation (N=152)	Subthalamic Stimulation (N=147)	P Value†	Initially to Medical Therapy (N=117)	Initially to Deep-Brain Stimulation (N=121)	Directly to Deep-Brain Stimulation (N=61)	P Value†
Demographic or clinical							
Age							
Mean — yr	61.8±8.7	61.9±8.7	0.92	61.8±8.5	62.4±8.8	60.7±8.6	0.47
≥70 yr — no. (%)	35 (23.0)	34 (23.1)	0.99	27 (23.1)	31 (25.6)	11 (18.0)	0.54
Male sex — no. (%)	133 (87.5)	116 (78.9)	0.06	101 (86.3)	98 (81.0)	50 (82.0)	0.51
Patient at Veterans Affairs facility — no. (%)	90 (59.2)	85 (57.8)	0.82	73 (62.4)	73 (60.3)	29 (47.5)	0.14
Duration of use of medication for Parkinson's disease — yr	11.5±5.4	11.1±5.0	0.47	12.4±5.3	10.8±5.4	10.1±4.2	0.008
White race — no. (%)‡	148 (97.4)	139 (94.6)	0.25	111 (94.9)	117 (96.7)	59 (96.7)	0.75
Married — no. (%)	109 (71.7)	97 (66.0)	0.63	83 (70.9)	81 (66.9)	42 (68.9)	0.50
Living with family — no. (%)	127 (83.6)	113 (76.9)	0.23	93 (79.5)	100 (82.6)	47 (77.0)	0.89
Help from personal caregiver — no. (%)	63 (41.4)	74 (50.3)	0.13	59 (50.4)	56 (46.3)	22 (36.1)	0.18
Family history of Parkinson's disease — no. (%)	37 (24.3)	38 (25.9)	0.79	25 (21.4)	32 (26.4)	18 (29.5)	0.42
Functional status							
Score on Unified Parkinson Disease Rating Scale§							
I (mentation, behavior, and mood; range, 0–16)	2.5±1.9	2.9±2.0	0.07	3.0±2.1	2.6±2.0	2.3±1.7	0.12
II (activities of daily living; range, 0–52)	19.1±5.8	19.0±6.1	0.92	19.5±5.7	19.1±5.9	18.2±6.3	0.35
III (motor function without medication; range, 0–108) (primary outcome)	41.8±13.1	43.0±15.0	0.46	41.2±12.8	43.0±13.5	43.8±17.2	0.43
IV (complication of therapy; range, 0–23)	8.8±3.1	9.0±2.9	0.51	8.8±3.1	9.2±3.0	8.5±3.1	0.33
Score on Hoehn and Yahr scale without medication (disability; range, 0–5)§	3.3±0.9	3.4±0.9	0.47	3.3±0.9	3.4±0.9	3.2±1.0	0.70
Score on Schwab and England scale without medication (activities of daily living; range, 0–100)¶	51.2±20.5	50.7±20.1	0.85	50.2±18.5	50.4±20.5	53.6±23.0	0.52
Self-reported motor function with medication — hr/day‖							
Good motor function	6.5±2.9	7.0±3.1	0.15	6.9±3.3	6.4±2.7	6.9±2.8	0.31
Motor function with troublesome dyskinesia	4.4±3.3	4.0±3.0	0.28	4.1±3.2	4.4±3.1	4.0±3.3	0.69
Quality of life							
Score on Parkinson's Disease Questionnaire–39 Items (range, 0–100)§							
Mobility	57.0±22.3	61.6±20.6	0.06	57.5±22.0	61.1±21.0	58.9±21.8	0.43
Activities of daily living	55.0±18.6	55.7±18.1	0.77	56.4±18.6	55.0±17.6	54.0±19.4	0.70

Emotional well-being	36.5±18.9	41.1±18.6	0.04	38.0±18.8	38.4±19.3	41.0±17.9	0.60
Social support	23.8±17.2	30.1±19.3	0.003	28.2±19.0	26.9±19.6	24.5±15.1	0.46
Cognition	39.8±16.7	44.1±17.0	0.03	44.1±16.9	40.4±17.8	40.7±15.2	0.21
Neurocognitive status							
Score on Beck Depression Inventory II (range, 0–63)§	10.4±7.8	11.2±7.1	0.40	10.1±6.7	11.3±8.7	11.2±6.3	0.44
Score on Mattis Dementia Rating Scale (range, 0–144)¶	137.5±4.8	137.2±5.1	0.60	138.2±4.5	136.7±4.8	137.1±5.7	0.06
Score on Wechsler Adult Intelligence Scales III¶**							
Processing speed index (range, 54–150)	91.3±13.8	90.0±13.8	0.41	90.4±14.0	91.0±13.9	90.5±13.6	0.94
Working memory index (range, 50–150)	100.8±13.0	99.3±13.7	0.34	99.6±13.9	101.2±13.3	98.9±12.6	0.51
Verbal fluency T score (no. of words)¶††							
Phonemic (sounds of words; range, 7–100)	46.6±12.0	44.9±12.1	0.25	46.3±11.8	45.7±12.1	44.9±12.7	0.75
Semantic (names of animals; range, 0–100)	50.4±10.6	47.0±12.4	0.01	47.6±11.7	50.9±11.3	46.6±11.8	0.03
Hopkins Verbal Learning Test T score (no. of words)¶††							
Total (learning and memory; range, 19–75)	40.7±10.6	38.0±11.3	0.04	40.4±11.2	38.9±11.3	38.2±10.0	0.39
Delayed recall (range, 19–65)	38.5±13.4	37.0±13.3	0.34	37.8±13.5	37.3±13.3	38.7±13.1	0.79
Finger-tapping T score (average of left and right hands; range, 1–100)¶††	38.2±12.7	38.1±11.8	0.93	39.1±13.2	37.1±11.4	38.4±12.0	0.46
Score on Boston Naming Test (language; range, 0–60)¶	55.9±4.5	55.6±4.5	0.60	56.6±3.9	55.5±4.5	54.6±5.4	0.02
Wisconsin Card Sorting Test T score (perseverative response; range, 19–81)¶††	45.3±13.2	44.5±11.2	0.54	44.9±11.6	46.1±13.0	42.5±11.9	0.17
Stroop interference T score (range, 19–81)¶††	51.1±8.7	51.0±6.8	0.94	51.9±8.4	50.7±7.4	50.3±7.3	0.37
Brief Visuospatial Memory Test T score¶††							
Delayed recall (range, 19–38)	44.8±13.3	43.0±13.7	0.23	45.7±13.5	42.1±13.3	44.2±13.7	0.13
Total (range, 19–77)	40.2±12.4	39.7±12.9	0.75	41.0±12.4	39.0±12.5	39.8±13.1	0.47

* Plus–minus values are means ±SD.
† P values were calculated with the use of Student's t-test or analysis of variance for continuous variables and Fisher's exact test for categorical variables.
‡ Race was self-reported.
§ A higher score indicates worse functioning.
¶ A higher score indicates better functioning.
‖ The time with or without troublesome dyskinesia was calculated on the basis of patients' motor diaries. Troublesome dyskinesia was defined as involuntary twisting or turning movements, other than tremor, that were troubling to the patient.
** These scales are based on a norm mean of 100±15.
†† These scales are based on a norm mean of 50±10.

The enrollment of 300 patients was necessary for the comparison of the primary outcome. Analyses were performed with the use of SAS software, version 9.1. All statistical tests were two-sided, and a P value of 0.05 was considered to indicate statistical significance, with no formal correction for multiple comparisons.

RESULTS

PATIENTS

A total of 299 patients with Parkinson's disease were randomly assigned to undergo either bilateral pallidal stimulation (152 patients) or bilateral subthalamic stimulation (147 patients) (Fig. 1).

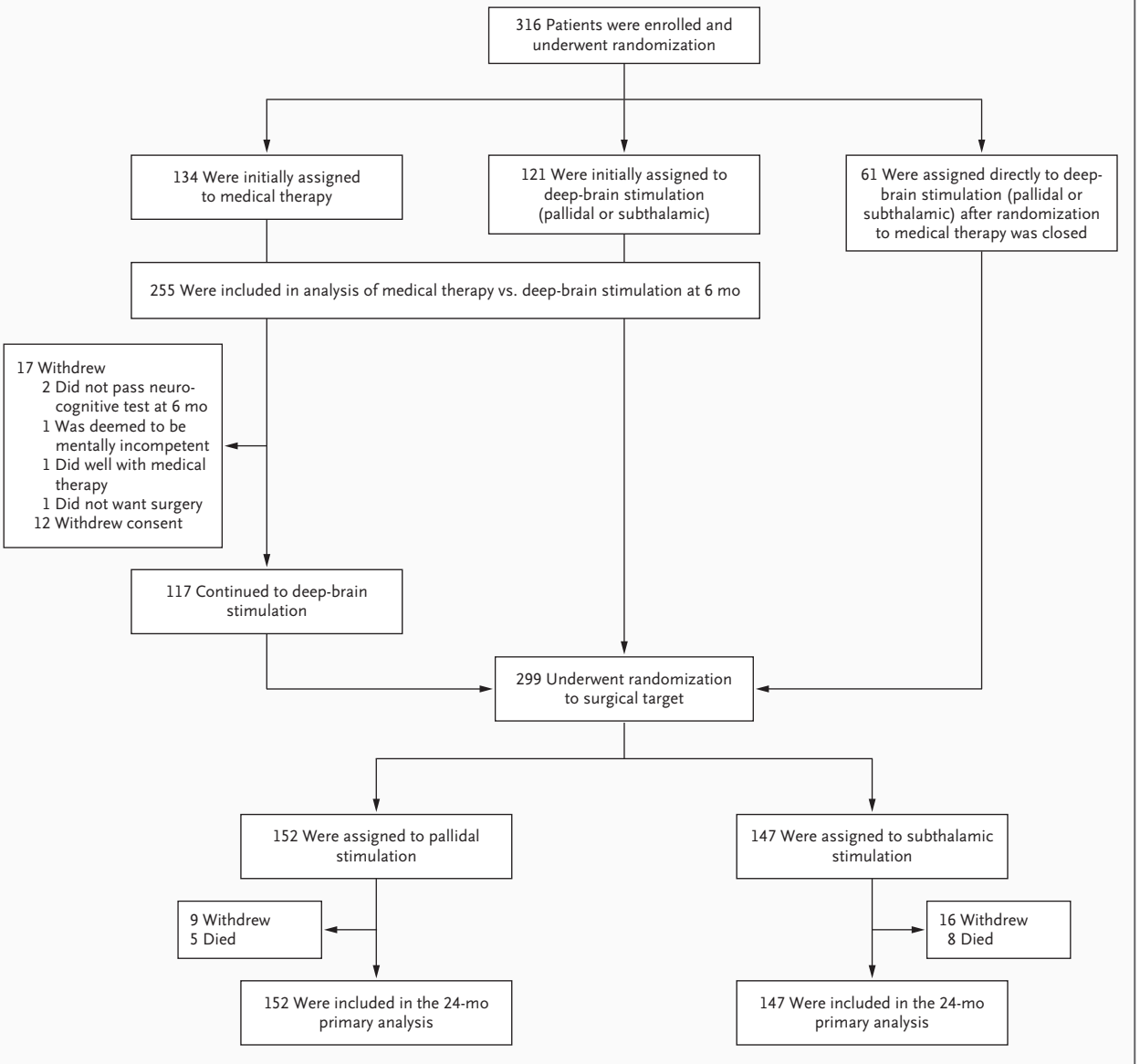

Figure 1. Enrollment and Outcomes in the Two Phases of the Study.

In the first phase of the study, 316 patients were randomly assigned to receive medical therapy or undergo deep-brain stimulation (targeting either the pallidal or subthalamic region) or were directly assigned to undergo deep-brain stimulation (after randomization to medical therapy was closed).[1] In the second phase, 117 of the patients who were originally assigned to receive medical therapy subsequently underwent a second randomization to undergo either pallidal or subthalamic stimulation.

The clinical characteristics of the three groups of patients — those originally assigned to receive medical therapy as compared with deep-brain stimulation, those assigned to undergo deep-brain stimulation as compared with medical therapy, and those assigned to bypass the comparison between medical therapy and deep-brain stimulation — were similar at baseline except for small differences in the number of years of receipt of medication for Parkinson's disease, scores on a test of verbal fluency (animal names), and scores on the Boston Naming Test (Table 1). The baseline characteristics of the two overall groups that underwent deep-brain stimulation were similar except for the scores on the PDQ-39 subscales of emotional well-being (P=0.04), social support (P=0.003), and cognition (P=0.03); verbal fluency (animal names) (P=0.01); and the total score on the Hopkins Verbal Learning Test (P=0.04).

Seventeen patients in the medical-therapy group withdrew before they were randomly assigned to undergo deep-brain stimulation. As compared with the 117 patients in the medical-therapy group who remained in the study and underwent deep-brain stimulation, the 17 patients who withdrew were older (≥70 years of age, 59% vs. 23%), were more likely to be women (47% vs. 14%), were less likely to live with family (53% vs. 80%), and had worse UPDRS-III motor scores (50.8 vs. 44.3 points with medication and 45.6 vs. 42.9 without medication). A total of 38 patients did not complete the 24-month assessment: 25 patients withdrew (9 in the pallidal-stimulation group and 16 in the subthalamic-stimulation group) and 13 died (5 in the pallidal-stimulation group and 8 in the subthalamic-stimulation group). As compared with patients who completed the 24-month follow-up, those who did not were older (67.7 years vs. 61.0 years), were less likely to live with family (74% vs. 81%), and had higher UPDRS-III motor scores (27.3 vs. 21.8 with medication and 45.5 vs. 42.0 without medication). A total of 279 patients completed the 6-month evaluation.

MOTOR FUNCTION

The primary outcome, the change in the UPDRS-III score at 24 months with deep-brain stimulation and without medication, did not differ significantly according to the surgical target, with a reduction of 11.8 points in the pallidal-stimulation group and of 10.7 points in the subthalamic-stimulation group (difference, –1.1 points; 95% confidence interval, –4.3 to 2.1; P=0.50) (Table 2). With both stimulation and medication, patients undergoing pallidal stimulation had a slight improvement in motor function (a reduction of 1.2 points in the UPDRS-III score), whereas patients undergoing subthalamic stimulation had a slight worsening (an increase of 0.8 points) (P=0.09) (Table 2). Without stimulation or medication, the mean change from baseline in motor function differed significantly between the two study groups, with patients undergoing pallidal stimulation having improvement (a reduction of 3.7 points in the UPDRS-III score) and patients undergoing subthalamic stimulation having deterioration (an increase of 2.2 points) (P<0.001).

At 24 months, two thirds of the patients in the two study groups had at least a 5-point improvement in the UPDRS-III score (a minimal measurement of clinically important change[11]) while receiving stimulation without medication; 7% of patients undergoing pallidal stimulation and 12% of patients undergoing subthalamic stimulation had a decline of at least 5 points (P=0.10). The primary outcome was stable over the 24-month follow-up period, as were UPDRS-III scores for the other combinations of assessments (with or without stimulation and with or without medication). Analysis of mixed-effects models of the response over time showed results that were consistent with those in the intention-to-treat population (Table 2).

Other approaches for handling missing data — which included analysis of complete data only, assignment of zero (no change) for any missing data, and application of the worst-case scenario (assignment of the best scores at baseline and the worst scores at 24 months for missing data) — were performed. Results were consistent with the intention-to-treat and mixed-model analyses.

MOTOR DIARY, STAND–WALK–SIT TEST, AND MEDICATION USE

On the basis of patients' diary entries with respect to four states — good motor function, motor function with troublesome dyskinesia, poor motor function, or asleep — the amount of time that they spent per 24 hours in each of these states did not differ significantly between the two study groups (Table 3). Changes in scores on the stand–walk–sit test differed between the two study groups only when patients were not receiving either stimulation or medication, with the

Table 2. Primary Outcome and Other Motor Scores on the Unified Parkinson's Disease Rating Scale.*

Variable	Mean Score†		Mean Change from Baseline at 24 Mo (95% CI)		P Value	Mean Change from 6 Mo at 24 Mo (95% CI)		P Value
	Pallidal Stimulation	Subthalamic Stimulation	Pallidal Stimulation	Subthalamic Stimulation		Pallidal Stimulation	Subthalamic Stimulation	
With stimulation, without medication‡								
Intention-to-treat analysis								
Baseline	41.8±13.1	43.0±15.0						
6 Mo	30.0±13.7	32.2±16.2	−11.7 (−13.8 to −9.6)	−10.6 (−12.8 to −8.5)	0.48			
24 Mo	30.0±14.2	32.1±15.6	−11.8 (−14.1 to −9.5)	−10.7 (−12.9 to −8.5)	0.50	0 (1.5 to 1.5)	0 (−1.5 to 1.4)	0.97
Mixed-effects model								
Baseline	41.8 (39.6 to 44.1)	43.0 (40.7 to 45.2)						
6 Mo	28.4 (26.1 to 30.7)	29.9 (27.6 to 32.3)	−13.4 (−15.6 to −11.2)	−13.0 (−15.3 to −10.7)	0.81			
24 Mo	28.7 (26.4 to 30.9)	30.1 (27.7 to 32.4)	−13.1 (−15.5 to −10.8)	−12.9 (−15.4 to −10.4)	0.90	0.3 (1.4 to 2.0)	0.1 (−1.7 to 2.0)	0.90
With stimulation, with medication								
Intention-to-treat analysis								
Baseline	22.6±11.9	22.4±11.9						
6 Mo	20.3±10.4	21.4±12.5	−2.3 (−3.9 to −0.6)	−1.0 (−2.4 to 0.4)	0.25			
24 Mo	21.4±11.8	23.2±12.0	−1.2 (−2.8 to 0.4)	0.8 (−0.9 to 2.4)	0.09	1.1 (0.3 to 2.5)	1.8 (0.5 to 3.0)	0.46
Mixed-effects model								
Baseline	22.6 (20.7 to 24.5)	22.4 (20.5 to 24.4)						
6 Mo	19.9 (18.1 to 21.7)	20.6 (18.7 to 22.4)	−2.7 (−4.4 to −1.0)	−1.9 (−3.6 to −0.1)	0.52			
24 Mo	21.2 (19.3 to 23.1)	22.9 (20.9 to 24.9)	−1.4 (−3.1 to 0.4)	0.4 (−1.4 to 2.3)	0.17	1.3 (0.1 to 2.8)	2.3 (0.7 to 3.9)	0.37

Without stimulation, without medication							
Intention-to-treat analysis							
Baseline	41.8±13.1	43.0±15.0					
6 Mo	36.9±13.8	42.9±16.0	–4.8 (–6.9 to –2.7)	0 (–1.9 to 2.0)	<0.001		
24 Mo	38.1±14.6	45.1±14.6	–3.7 (–5.9 to –1.4)	2.2 (–0 to 4.5)	<0.001	1.2 (0.6 to 3.0)	2.2 (0.5 to 3.8)	0.43
Mixed-effect model							
Baseline	41.8 (39.5 to 44.0)	43.0 (40.7 to 45.2)					
6 Mo	36.2 (33.7 to 38.7)	42.6 (40.1 to 45.2)	–5.6 (–7.8 to –3.3)	–0.3 (–2.6 to 2.0)	0.001		
24 Mo	37.7 (35.4 to 40.1)	44.8 (42.3 to 47.3)	–4.0 (–6.4 to –1.6)	1.9 (–0.7 to 4.4)	0.001	1.5 (0.5 to 3.6)	2.2 (–0.1 to 4.4)	0.69

* Scores on the Unified Parkinson's Disease Rating Scale range from 0 to 108 points, with higher scores indicating more severe motor symptoms. All evaluators were unaware of study-group assignments. P values for interactions between time and study group in the mixed-effects analyses of motor scores were as follows: P=0.97 for the evaluation with stimulation and without medication, P=0.37 for the evaluation with stimulation and with medication, and P=0.002 for the evaluation without stimulation and without medication. CI denotes confidence interval.
† Plus–minus values are means ±SD. Values in parentheses are 95% CIs.
‡ This mode of evaluation was the primary outcome.

group undergoing pallidal stimulation having significantly greater improvement than the group undergoing subthalamic stimulation (a reduction of 4.1 seconds and 0.2 seconds, respectively; P=0.005). The average medication use (levodopa equivalents) decreased more in the subthalamic-stimulation group (a reduction of 408 mg) than in the pallidal-stimulation group (a reduction of 243 mg, P=0.02).

QUALITY OF LIFE

After 24 months, the quality of life improved on six of eight subscales of the PDQ-39 in the two study groups, although the level of communication worsened slightly in both groups (Table 3). Social-support scores worsened slightly after pallidal stimulation but improved slightly after subthalamic stimulation. None of the between-group differences were significant.

NEUROCOGNITIVE FUNCTION AND MOOD

At the 24-month follow-up, patients in the two study groups had similarly slight decrements in all measures of neurocognitive function, except for the processing speed index (as measured on the Wechsler Adult Intelligence Scales III), in which the extent of decline was greater for the group undergoing subthalamic stimulation than for the group undergoing pallidal stimulation (P=0.03) (Table 3). Group differences on the digit symbol visuomotor subtest accounted for this effect. Overall scores on the Beck Depression Inventory II improved slightly for the group undergoing pallidal stimulation but worsened slightly for the group undergoing subthalamic stimulation (P=0.02).

ADVERSE EVENTS

A total of 335 serious adverse events occurred in 77 patients undergoing pallidal stimulation and in 83 undergoing subthalamic stimulation (Table 4). There were no significant between-group differences in the frequency or type of serious adverse events. Ninety-nine percent of these events were resolved by the conclusion of the 24-month study follow-up. A total of 3356 moderate or severe adverse events — 1601 in the pallidal-stimulation group and 1755 in the subthalamic stimulation group — were reported over the 24-month period (Table 4). Adverse events did not differ significantly in frequency or type between the two study groups at 24 months.

Thirteen deaths occurred during follow-up (five among patients undergoing pallidal stimulation

Table 3. Changes in Secondary Outcomes at 24 Months.*

Outcome	Pallidal Stimulation (N=152)		Subthalamic Stimulation (N=147)		Pallidal vs. Subthalamic Stimulation	
	Baseline	24 Mo	Baseline	24 Mo	Difference (95% CI)	P Value†
Functional status						
Score on Unified Parkinson's Disease Rating Scale‡						
I (mentation, behavior, and mood; range, 0–16)	2.5±1.9	2.9±2.2	2.9±2.0	3.6±2.3	−0.2 (−0.7 to 0.3)	0.39
II (activities of daily living; range, 0–52)	19.1±5.8	15.8±6.2	19.0±6.1	16.8±6.8	−1.1 (−2.6 to 0.4)	0.15
IV (complications of therapy; range, 0–23)	8.8±3.1	5.4±2.7	9.0±2.9	5.1±2.9	0.5 (−0.3 to 1.3)	0.26
Score on Hoehn and Yahr scale without medication (disability; range, 0–5)‡	3.3±0.9	3.0±1.0	3.4±0.9	3.1±0.9	0 (−0.3 to 0.2)	0.77
Score on Schwab and England scale without medication (activities of daily living; range, 0–100)§	51.2±20.5	66.0±21.6	50.7±20.1	62.9±22.1	2.6 (−2.9 to 8.2)	0.35
Stand–walk–sit test (sec)¶						
With stimulation, with medication	18.0±12.3	18.5±12.2	17.4±8.1	19.4±12.5	−2.0 (−4.6 to 0.6)	0.13
With stimulation, without medication	27.2±17.0	22.9±18.4	26.1±13.3	22.9±16.7	−2.3 (−5.2 to 0.6)	0.12
Without stimulation, without medication	27.2±17.0	22.7±15.2	26.1±13.3	26.6±17.2	−3.9 (−6.5 to −1.2)	0.005
Levodopa equivalents (mg)‖	1361±545	1118±562	1295±585	887±545	165.4 (21.7 to 309.1)	0.02
Self-reported motor function — hr/day**						
Good motor function	6.5±2.9	11.4±4.2	7.0±3.1	11.0±4.4	0.9 (−0.1 to 2.0)	0.09
Motor function with troublesome dyskinesia	4.4±3.3	1.2±2.4	4.0±3.0	1.4±2.4	−0.5 (−1.4 to 0.3)	0.20
Poor motor function	5.8±2.6	3.1±3.2	5.9±2.7	3.4±3.7	−0.2 (−1.1 to 0.6)	0.61
Asleep	7.3±1.7	8.2±1.8	7.1±2.1	8.1±2.1	−0.2 (−0.7 to 0.3)	0.46
Quality of life						
Score on Parkinson's Disease Questionnaire–39 Items (range, 0–100)‡						
Mobility	57.0±22.3	46.6±25.3	61.6±20.6	54.0±24.5	−2.3 (−7.6 to 3.1)	0.40
Activities of daily living	55.0±18.6	41.4±20.7	55.7±18.1	46.6±23.7	−4.4 (−9.3 to 0.5)	0.08
Emotional well-being	36.5±18.9	33.4±19.1	41.1±18.6	39.1±21.1	−1.2 (−5.6 to 3.2)	0.58
Stigma	38.7±25.3	28.2±22.4	42.1±24.6	30.7±25.3	1.0 (−4.5 to 6.4)	0.73
Social support	23.8±17.2	26.0±18.6	30.1±19.3	29.4±20.1	3.1 (−1.2 to 7.4)	0.16
Cognition	39.8±16.7	38.9±18.4	44.1±17.0	43.5±19.3	−0.4 (−4.2 to 3.5)	0.85
Communication	44.7±19.5	48.5±20.5	47.8±18.6	53.1±22.1	−1.5 (−6.3 to 3.3)	0.54
Bodily discomfort	48.1±21.1	40.5±21.8	52.8±23.4	46.3±24.0	−1.0 (−5.6 to 3.5)	0.65
Single index	42.8±13.6	38.0±15.3	46.9±12.6	42.7±15.6	−0.6 (−3.6 to 2.4)	0.69

Neurocognitive status						
Score on Beck Depression Inventory (range, 0–63)‡	10.4±7.8	9.8±7.3	11.2±7.1	12.5±8.5	−1.9 (−3.6 to −0.2)	0.02
Total score on Mattis Dementia Rating Scale (range, 0–144)§	137.5±4.8	135.0±9.8	137.2±5.1	133.6±9.6	1.0 (−0.9 to 3.0)	0.29
Score on Wechsler Adult Intelligence Scales III§ ††						
Processing speed index (range, 54–150)	91.3±13.8	88.3±14.8	90.0±13.8	84.1±13.0	2.5 (0.3 to 4.7)	0.03
Working memory index (range, 50–150)	100.8±13.0	97.0±13.4	99.3±13.7	94.1±15.3	1.1 (−0.8 to 3.0)	0.27
Verbal fluency T score§‡‡						
Phonemic (sounds of words; range, 7–100)	46.6±12.0	41.8±11.9	44.9±12.1	39.0±12.0	1.1 (−1.2 to 3.4)	0.33
Semantic (names of animals; range, 0–100)	50.4±10.6	44.7±12.4	47.0±12.4	41.2±13.2	0 (−2.8 to 2.8)	0.99
Hopkins Verbal Learning Test T score§ ‡‡						
Total (learning and memory; range, 19–75)	40.7±10.6	38.5±10.7	38.0±11.3	37.3±10.9	−1.4 (−3.7 to 0.9)	0.24
Delayed recall (range, 19–65)	38.5±13.4	37.5±12.4	37.0±13.3	36.3±12.7	−0.3 (−3.1 to 2.5)	0.84
Finger-tapping T score (average of left and right hands; range, 1–100)§‡‡	38.2±12.7	38.0±12.6	38.1±11.8	35.9±13.0	1.9 (−0.9 to 4.8)	0.18
Score on Boston Naming Test (language; range, 0–60)§	55.9±4.5	55.7±5.0	55.6±4.5	55.2±5.5	0.2 (−0.5 to 0.8)	0.57
Wisconsin Card Sorting Test T score (perseverative response; range, 19–81)§‡‡	45.3±13.2	43.0±12.2	44.5±11.2	43.4±12.3	−1.3 (−4.3 to 1.6)	0.38
Stroop interference T score (range, 19–81)§‡‡	51.1±8.7	51.0±7.7	51.0±6.8	50.1±7.4	0.8 (−1.0 to 2.7)	0.38
Brief Visuospatial Memory Test T score§‡‡						
Delayed recall (range, 19–68)	44.8±13.3	41.0±13.4	43.0±13.7	41.1±14.1	−1.9 (−4.7 to 0.8)	0.17
Total (range, 19–77)	40.2±12.4	38.6±12.1	39.7±12.9	38.3±12.2	−0.2 (−2.7 to 2.3)	0.87

* Plus–minus values are means ±SD.
† P values are for changes in scores from baseline to 24 months in the group undergoing pallidal stimulation, as compared with those undergoing subthalamic stimulation.
‡ A higher score indicates worse functioning.
§ A higher score indicates better functioning.
¶ Evaluations in which brain stimulation was turned on or off apply only to the 24-month examinations, since baseline evaluations were conducted before deep-brain stimulation surgery.
‖ Levodopa equivalents were based on the following calculations: 100 mg of levodopa equals 133 mg of controlled-release levodopa, 10 mg of bromocriptine, 1 mg of pergolide, 3 mg of ropinirole, and 1 mg of pramipexole.[10]
** The time with or without troublesome dyskinesia was calculated on the basis of patients' motor diaries.
†† These scales are based on a norm mean of 100±15.
‡‡ These scales are based on a norm mean of 50±10.

Table 4. Adverse Events at 24 Months.*

Event	Pallidal Stimulation (N=152)	Subthalamic Stimulation (N=147)	P Value
	no. (%)		
Serious adverse event†			
Any	77 (50.7)	83 (56.5)	0.35
Implantation-site infection	12 (7.9)	11 (7.5)	0.99
Fall	5 (3.3)	13 (8.8)	0.05
Pneumonia	8 (5.3)	4 (2.7)	0.38
Confusional state	2 (1.3)	5 (3.4)	0.28
Medical-device complication	2 (1.3)	4 (2.7)	0.44
Lumbar spine stenosis	3 (2.0)	2 (1.4)	0.99
Mental status change	4 (2.6)	1 (0.7)	0.37
Osteoarthritis	3 (2.0)	2 (1.4)	0.99
Syncope	1 (0.7)	4 (2.7)	0.21
Depression	4 (2.6)	1 (0.7)	0.37
Adverse drug reaction	2 (1.3)	2 (1.4)	0.99
Coronary artery disease	1 (0.7)	3 (2.0)	0.36
Dyskinesia	1 (0.7)	3 (2.0)	0.36
Gastroesophageal reflux disease	2 (1.3)	2 (1.4)	0.99
Inguinal hernia	2 (1.3)	2 (1.4)	0.99
Suicidal depression	2 (1.3)	1 (0.7)	0.99
Cerebral hemorrhage	1 (0.7)	2 (1.4)	0.62
Stroke	0	3 (2.0)	0.12
Intracranial hemorrhage	3 (2.0)	0	0.25
Moderate or severe adverse event‡			
Fall	58 (38.2)	63 (42.9)	0.41
Gait disturbance	49 (32.2)	45 (30.6)	0.80
Depression	40 (26.3)	54 (36.7)	0.06
Balance disorder	47 (30.9)	44 (29.9)	0.90
Speech problem	43 (28.3)	51 (34.7)	0.26
Freezing phenomenon	48 (31.6)	35 (23.8)	0.16
Bradykinesia	36 (23.7)	32 (21.8)	0.78
Motor dysfunction	36 (23.7)	31 (21.1)	0.68
Dyskinesia	34 (22.4)	38 (25.9)	0.50
Dystonia	34 (22.4)	31 (21.1)	0.89
Confused state	30 (19.7)	33 (22.4)	0.57

* All events are listed according to the definitions used in the *Medical Dictionary for Regulatory Activities,* version 11.0, for serious adverse events and moderate or severe adverse events.

† All listed serious adverse events were reported in four or more patients, except for four events that are critical in this population — suicidal depression, cerebral hemorrhage, stroke, and intracranial hemorrhage — each of which occurred in three patients.

‡ All listed moderate or severe adverse events were reported in at least 20% of the patients. A moderate event is defined as one that may interfere with normal activity and lead to the consideration of medical intervention or close follow-up. A severe event poses substantial risk to patient's health and is likely to require medical intervention or close follow-up.

and eight among those undergoing subthalamic stimulation). One death in the subthalamic-stimulation group was related directly to the surgical procedure (an intracranial hemorrhage 24 hours after surgery). One patient undergoing pallidal stimulation committed suicide; two patients undergoing subthalamic stimulation attempted suicide and one other patient undergoing pallidal stimulation had suicidal ideation. Other deaths were attributed to aspiration pneumonia (one in the pallidal-stimulation group and two in the subthalamic-stimulation group). Among patients undergoing pallidal stimulation, one patient each died from myocardial infarction with sepsis, intestinal perforation with sepsis, and breast cancer. Among patients undergoing subthalamic stimulation, one patient each died from arteriosclerotic heart disease, sepsis with multiple organ failure, drug toxicity, injuries sustained in a motorcycle accident, and severe Parkinson's disease with cachexia.

STIMULATION SETTINGS

At 24 months, the average stimulation amplitudes differed significantly between the group undergoing pallidal stimulation (3.95 V) and the group undergoing subthalamic stimulation (3.16 V) ($P<0.001$); average pulse widths were 95.7 μsec and 75.9 μsec, respectively ($P=0.001$). Frequencies did not differ significantly (168 Hz and 165 Hz, respectively).

DISCUSSION

Deep-brain stimulation improved motor function in patients with Parkinson's disease who underwent either pallidal or subthalamic stimulation, with no significant difference between the two surgical targets during 24 months of follow-up, as assessed by scores on the UPDRS-III among patients while they were not taking medication. To our knowledge, bilateral pallidal stimulation has been directly compared with subthalamic stimulation in only one previous randomized trial.[12] The findings in this trial, which involved 20 patients, were similar to our results. A meta-analysis of studies of pallidal and subthalamic stimulation also showed that motor function improved in a similar manner for the two target regions at 6 months.[13] A recent study of unilateral pallidal stimulation versus unilateral subthalamic stimulation also showed equivalent motor outcomes.[14]

Concern has been expressed regarding the long-term durability of pallidal stimulation for Parkinson's disease.[15] The efficacy of bilateral pallidal stimulation has been reported to decrease over time in several small series.[16-19] Other reports describe stable responses to pallidal stimulation for up to 3 years.[20-23] In several studies, patients in whom pallidal stimulation failed had a successful conversion to subthalamic stimulation.[17,18] Whether failure of long-term subthalamic stimulation can be salvaged by conversion to pallidal stimulation is not known. We did not observe a significant decrement in motor function during 24 months of follow-up in either of our two treatment groups. Extended follow-up will be important to determine whether responses to stimulation at the two targets are stable over longer periods of time.

Nonmotor function is an important determinant of quality of life in patients with Parkinson's disease and should be a consideration in therapy selection.[24,25] A recent study comparing unilateral pallidal stimulation with unilateral subthalamic stimulation showed similar improvement in motor function but greater improvement in quality-of-life measures in the group undergoing pallidal stimulation,[25] an outcome that was postulated to reflect a higher incidence of adverse postoperative neurocognitive and mood changes in the group undergoing subthalamic stimulation. In our study, significant differences between the two study groups on measures of neurocognitive function and mood were limited to one measure of visuomotor speed and overall self-reported symptoms on a depression inventory, and we did not observe a significant difference between the two study groups in quality of life, as measured by the PDQ-39. The differences in neurocognitive and mood changes and quality-of-life measures that have been reported for patients after unilateral pallidal stimulation, as compared with subthalamic stimulation,[25] might reflect differences in the populations that were studied, differences in clinical effects of unilateral versus bilateral deep-brain stimulation, or differences related to the pharmacologic treatment of patients whose symptoms of Parkinson's disease are treated by unilateral stimulation.

We observed differences between pallidal stim-

ulation and subthalamic stimulation on several secondary measures in addition to neurocognitive and mood outcomes, but these findings should be interpreted cautiously. We did not adjust for repeated significance tests, and the differences we observed in secondary outcomes may have limited clinical significance. While patients were not receiving stimulation or medication, UPDRS-III scores and stand–walk–sit times were significantly better for patients undergoing pallidal stimulation than for those undergoing subthalamic stimulation. This relative advantage of pallidal stimulation probably reflects a longer "washout" period after deactivation of the stimulation systems[12] and is not important clinically because patients are unlikely to deactivate their stimulation systems.

The use of dopaminergic medications decreased more in patients undergoing subthalamic stimulation than in those undergoing pallidal stimulation on average. This difference may be an important consideration not only for patients who have side effects, in whom a reduction of medications may contribute to a better quality of life, but also for those in whom a reduction of medications may not be desirable.[13]

Stimulation amplitudes and pulse widths were lower on average for subthalamic stimulation than for pallidal stimulation, allowing for potentially longer intervals between pulse-generator replacement among patients undergoing subthalamic stimulation, with an attendant reduction in long-term costs of therapy and a reduction in risks associated with surgical replacement of pulse generators. The difference in amplitudes we observed contrasts with that reported in another large (nonrandomized, open-label) series involving patients undergoing either pallidal stimulation or subthalamic stimulation, in which average amplitudes for the two types of neurostimulation differed by only 0.2 V at 1 year and by 0.1 V at 3 to 4 years postoperatively.[23] Improvements in pulse-generator technology are likely to make this factor less important in the future.

Improvement in motor function as measured by UPDRS-III motor scores did not differ significantly according to the target of deep-brain stimulation, and we cannot conclude that one target is superior to the other on the basis of this measure. Both sites are feasible targets. The absence of a difference in motor outcomes in the two study groups should serve to reassure clinicians that the choice of target need not focus solely on improvement in motor function. The selection of the target can reasonably take into consideration the constellation of motor and nonmotor symptoms that define quality of life for patients with Parkinson's disease. Such selection can also depend on the goals of deep-brain stimulation (e.g., medication reduction) and the physician's preference for a target on the basis of experience or technical considerations associated with preoperative radiographic and intraoperative electrophysiological target localization and postoperative programming and management.

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APPENDIX

The authors' affiliations are as follows: the Iowa City Veterans Affairs (VA) Medical Center (K.A.F.) and the University of Iowa Health Care (G.S.) — both in Iowa City; the University of Nebraska Medical Center, Omaha (K.A.F.); the Center for Management of Complex Chronic Care (F.M.W.) and the Cooperative Studies Coordinating Center, Hines VA Hospital (K.H., P.L., D.J.R.) — both in Hines and Loyola University Stritch School of Medicine, Maywood (F.M.W.) — all in Illinois; University of Pennsylvania Health System (M.S., S.H., G.B.) and the Philadelphia VA Medical Center (M.S., J.E.D., G.B.) — both in Philadelphia; the VA Cooperative Studies Program, Clinical Research Pharmacy, Albuquerque, NM (C.L.H.); San Francisco VA Medical Center and University of California at San Francisco, San Francisco (W.J.M., J.R., P.A.S.); the University of Michigan Medical Center, Ann Arbor (O.S.); the National Institute of Neurological

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REFERENCES

1. 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.
2. 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.
3. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427-42.
4. Langston JW, Widner H, Goetz CG, et al. Core Assessment Program for Intracerebral Transplantations (CAPIT). Mov Disord 1992;7:2-13.
5. Fahn S, Elton RL, UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Goldstein M, eds. Recent developments in Parkinson's disease. Vol. 2. Florham Park, NJ: Macmillan Health Care Information, 1987:153-64.
6. Schwab RS, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldsom ML, eds. Third symposium on Parkinson's disease. Edinburgh: Livingstone, 1969:152-7.
7. Peto V, Jenkinson C, Fitzpatrick R. PDQ-39: a review of the development, validation and application of a Parkinson's disease quality of life questionnaire and its associated measures. J Neurol 1998;245:Suppl 1:S10-S14.
8. Hauser RA, Deckers F, Lehert P. Parkinson's disease home diary: further validation and implications for clinical trials. Mov Disord 2004;19:1409-13.
9. Goetz CG, Stebbins GT, Blasucci LM, Grobman MS. Efficacy of a patient-training videotape on motor fluctuations for on-off diaries in Parkinson's disease. Mov Disord 1997;12:1039-41.
10. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349:1925-34.
11. Schrag A, Sampaio C, Counsell N, Poewe W. Minimal clinically important change on the Unified Parkinson's Disease Rating Scale. Mov Disord 2006;21:1200-7.
12. Anderson VC, Burchiel KJ, Hogarth P, Favre J, Hammerstad JP. Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. Arch Neurol 2005;62:554-60.
13. Weaver F, Follett K, Hur K, Ippolito D, Stern M. Deep brain stimulation in Parkinson disease: a metaanalysis of patient outcomes. J Neurosurg 2005;103:956-67.
14. Okun MS, Fernandez HH, Wu SS, et al. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. Ann Neurol 2009;65:586-95.
15. Volkmann J. Deep brain stimulation for the treatment of Parkinson's disease. J Clin Neurophysiol 2004;21:6-17.
16. Barcia-Salorio JL, Roldan R, Talamantes F, Fascual-Leone A. Electrical inhibition of basal ganglia nuclei in Parkinson's disease: long-term results. Stereotact Funct Neurosurg 1999;72:202-7.
17. Houeto JL, Bejjani PB, Damier P, et al. Failure of long-term pallidal stimulation corrected by subthalamic stimulation in PD. Neurology 2000;55:728-30.
18. Volkmann J, Allert N, Voges J, et al. Long-term results of bilateral pallidal stimulation in Parkinson's disease. Ann Neurol 2004;55:871-5.
19. Ghika J, Villemure J-G, Fankhauser H, et al. Efficiency and safety of bilateral contemporaneous pallidal stimulation (deep brain stimulation) in levodopa-responsive patients with Parkinson's disease with severe motor fluctuations: a 2-year review. J Neurosurg 1998;89:713-8.
20. Durif F, Lemaire J-J, Debilly B, Dordain G. Long-term follow-up of globus pallidus internalis in Parkinson's disease. Mov Disord 2002;17:803-7.
21. Gross C, Rougier A, Guehl D, Boraud T, Julien J, Bioulac B. High-frequency stimulation of the globus pallidus chronic stimulation in Parkinson's disease: a study of seven cases. J Neurosurg 1997;87:491-8.
22. Lyons KE, Wilkinson SB, Tröster AI, Pahwa R. Long-term efficacy of globus pallidus stimulation for the treatment of Parkinson's disease. Stereotact Funct Neurosurg 2002;79:214-20.
23. Rodriguez-Oroz MC, Obeso JA, Lang AE, et al. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. Brain 2005;128:2240-9.
24. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 2000;69:308-12.
25. Zahodne LB, Okun MS, Foote KD, et al. Greater improvement in quality of life following unilateral deep brain stimulation surgery in the globus pallidus as compared to the subthalamic nucleus. J Neurol 2009;256:1321-9.