Bilateral Deep Brain Stimulation vs Best Medical Therapy for Patients With Advanced Parkinson Disease

A Randomized Controlled Trial

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Context Deep brain stimulation is an accepted treatment for advanced Parkinson disease (PD), although there are few randomized trials comparing treatments, and most studies exclude older patients.

Objective To compare 6-month outcomes for patients with PD who received deep brain stimulation or best medical therapy.

Design, Setting, and Patients Randomized controlled trial of patients who received either deep brain stimulation or best medical therapy, stratified by study site and patient age (<70 years vs ≥70 years) at 7 Veterans Affairs and 6 university hospitals between May 2002 and October 2005. A total of 255 patients with PD (Hoehn and Yahr stage ≥2 while not taking medications) were enrolled; 25% were aged 70 years or older. The final 6-month follow-up visit occurred in May 2006.

Intervention Bilateral deep brain stimulation of the subthalamic nucleus (n=60) or globus pallidus (n=61). Patients receiving best medical therapy (n=134) were actively managed by movement disorder neurologists.

Main Outcome Measures The primary outcome was time spent in the "on" state (good motor control with unimpeded motor function) without troubling dyskinesia, using motor diaries. Other outcomes included motor function, quality of life, neurocognitive function, and adverse events.

Results Patients who received deep brain stimulation gained a mean of 4.6 h/d of on time without troubling dyskinesia compared with 0 h/d for patients who received best medical therapy (between group mean difference, 4.5 h/d [95% CI, 3.7-5.4 h/d]; $P<.001$). Motor function improved significantly ($P<.001$) with deep brain stimulation vs best medical therapy, such that 71% of deep brain stimulation patients and 32% of best medical therapy patients experienced clinically meaningful motor function improvements (≥5 points). Compared with the best medical therapy group, the deep brain stimulation group experienced significant improvements in the summary measure of quality of life and on 7 of 8 PD quality-of-life scores ($P<.001$). Neurocognitive testing revealed small decrements in some areas of information processing for patients receiving deep brain stimulation vs best medical therapy. At least 1 serious adverse event occurred in 49 deep brain stimulation patients and 15 best medical therapy patients ($P<.001$), including 39 adverse events related to the surgical procedure and 1 death secondary to cerebral hemorrhage.

Conclusion In this randomized controlled trial of patients with advanced PD, deep brain stimulation was more effective than best medical therapy in improving on time without troubling dyskinesias, motor function, and quality of life at 6 months, but was associated with an increased risk of serious adverse events.

Trial Registration clinicaltrials.gov Identifier: NCT00056563

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DEEP BRAIN STIMULATION IS the surgical intervention of choice when Parkinson disease (PD) motor complications are inadequately managed with medications. Ideal candidates have fluctuating motor symptoms or medication-related adverse effects, few comorbidities, and no cognitive or behavioral

For editorial comment see p 104.

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disorders.[1] This younger, healthier population reflects a selection bias observed in most deep brain stimulation studies.[2,3] The typical patient with PD is older and has other medical conditions.

Deep brain stimulation for PD entered widespread clinical use in the late 1990s and acceptance of this therapy has increased over the past 15 years. The attractiveness of deep brain stimulation is related in part to the fact that stimulation is adjustable and reversible.[4] However, recent reports highlighting unexpected behavioral effects of stimulation suggest that deep brain stimulation, while improving motor function, may have other less desirable consequences.[5,6] The popularity of deep brain stimulation belies the fact that its utility relative to medical therapy has been studied only in uncontrolled studies, with 1 recent exception.[7]

Deuschl et al[7] reported significant improvement in patient outcomes following deep brain stimulation of the subthalamic nucleus, but also pointed out that not all patients who received deep brain stimulation improved. Quality-of-life outcomes favored deep brain stimulation for 64% and favored medical therapy in 36% of PD pairs randomized to deep brain stimulation or medical therapy. Similarly, although deep brain stimulation resulted in improved motor functioning in 71% of pairs, the functioning was better in 27% of the cases for the medically treated patients.

The present study is, to our knowledge, the first large, multicenter, monitored, randomized controlled, blinded assessment trial to compare the benefits and risks of deep brain stimulation with those of best medical therapy for patients with PD who span a wide age range. It is the first phase of an ongoing study that also will compare outcomes based on a surgical target for deep brain stimulation (subthalamic nucleus vs globus pallidus) over 2 years. For the present study, the target sites were combined into a single group to address the question of the surgical vs the medical intervention.

METHODS

Study Sites and Patients

Seven Veterans Affairs and 6 affiliated university medical centers enrolled 255 patients between May 2002 and October 2005. Study sites were selected on a competitive basis and required the participation of a movement disorder neurologist, a surgeon with expertise in globus pallidus and subthalamic nucleus deep brain stimulation implants and microelectrode recording, and appropriate supportive services (eg, neuropsychologists). Patients with idiopathic PD were eligible if they were classified as Hoehn and Yahr stage 2 or greater while not taking medication[8]; were responsive to levodopa; had persistent disabling symptoms (eg, motor fluctuations, dyskinesia) despite medication; experienced 3 or more hours per 24-hour period with poor motor function or symptom control; were receiving stable medical therapy for 1 month or longer; and were aged 21 years or older. Exclusion criteria included atypical syndromes, previous surgery for PD, surgical contraindications, active alcohol or drug abuse, dementia,[9] or pregnancy. Patients were not required to have a caregiver. The study was approved by each site's institutional review board and patients provided written informed consent. Race/ethnicity information was collected to determine what proportion of study participants were in minority groups.

Randomization and Blinding

Randomization to deep brain stimulation or best medical therapy included stratification by study site and patient age ($<$70 years vs $\geq$70 years). Motor function assessments were conducted by raters blinded to treatment.

Interventions

Patients who received best medical therapy were managed actively by study movement disorder neurologists after randomization. Neurologists applied state-of-the-art care, including adjuvant medication, and made adjustments to the dosages, frequency, or timing of medication, and to nonpharmacological therapy (eg, physical, occupational, and speech therapy) as needed to achieve best symptom control and optimal functioning.

Patients who received deep brain stimulation were further randomized to subthalamic nucleus or globus pallidus targets and underwent surgery within 1 month. Patients were blinded to the target. The study was conducted under an investigational device exemption because the deep brain stimulation system (Kinetra system, Medtronic Inc, Minneapolis, Minnesota) was not approved for use by the US Food and Drug Administration when the study began. Patients underwent bilateral deep brain stimulation lead implantation while awake, during 1 procedure whenever possible; however, some patients returned for the second lead implant due to patient fatigue or technical issues. Lead implantation was accomplished using stereotactic frames (Leksell, Elekta, Stockholm, Sweden or CRW, Integra Radionics, Burlington, Massachusetts) with magnetic resonance imaging, computed tomographic guidance, or both. Initial targets were based on standard coordinates for subthalamic nucleus and globus pallidus.

Intraoperative microelectrode recording and test stimulation were mandatory to optimize uniformity of implant technique and target localization. Microelectrode recording was expected to demonstrate neuronal activity stereotypical for subthalamic nucleus or globus pallidus targets. Intraoperative test stimulation was performed to assess improvement of parkinsonian signs and occurrence of stimulation-induced adverse effects.

All surgeons had significant prestudy expertise with deep brain stimulation surgery and microelectrode recording involving the subthalamic nucleus and globus pallidus and used their clinical judgment to identify the best location for lead implantation. Lead position was revised from the original target at the discretion of the surgeon based on the results of microelectrode recording and test stimulation. The neu-

rostimulator was usually implanted (under general anesthesia) on the same day immediately following lead implantation. Once the stimulator was turned on, patients in the deep brain stimulation group received continuous stimulation. Patients returned as needed for stimulation-parameter adjustments using a standardized protocol to maximize symptom control and minimize adverse effects. Stimulation and medication adjustments were conducted by clinicians unblinded to treatment.

Study Procedures

Recruitment included referrals to study neurologists and patient self-referral. Informed consent and baseline assessments were obtained if initial review by the study nurse indicated the patient was eligible. Patients came to the clinic having stopped their PD medications the night before.[10] Patients completed the Mini-Mental State Examination[11] and those who scored less than 25 were excluded from the trial. The movement disorder neurologist completed the Unified Parkinson Disease Rating Scale (UPDRS)[12] motor subscale while the patient was not taking medication. A second neurologist, blinded to treatment, independently completed the motor subscale. To ensure blinded assessments during follow-up, all patients wore caps to cover evidence of possible cranial surgery and clothing to cover any incision for the neurostimulator. Patients then took their PD medications, and assessments were repeated 1 hour later by 1 neurologist. If patients had not attained their best functioning, additional medications could be taken to reach optimum functioning.

When the patient was taking medication, the movement disorder neurologist assessed the patient using the Hoehn and Yahr[8] and Schwab and England[13] scales. The patient performed the stand-walk-sit test[10] and completed the other UPDRS subscales[12] and the Parkinson Disease Questionnaire 39.[14] The nurse recorded usual medications taken and assessed the patient's physical health status and PD symptoms.

A neurocognitive test battery was administered by a neuropsychologist, usually on a different day than the motor assessments to reduce patient burden. Measures included the Mattis Dementia Rating Scale[9] and standardized tests of attention, working memory, visuomotor speed taken from the Wechsler Adult Intelligence Scales III, verbal associative fluency, other aspects of executive functioning (Stroop Test, Wisconsin Card Sorting Test) and language (Boston Naming Test), learning and memory (Brief Visuospatial Memory Test and Hopkins Verbal Learning Test, with alternate forms at each assessment), manual tapping speed, and mood.

Patients with advanced PD often experience motor function fluctuations throughout the day, resulting in periods of good symptom control or unimpeded motor function (classified as "on" time), and periods of poor symptom control and impaired motor function (classified as "off" time). On time may include involuntary movements (dyskinesia). Self-report motor diaries are a validated method to capture this information.[15] Training on diary completion was conducted by the nurse and included instructions and example diaries, review of a motor fluctuation videotape,[16] and completion of practice diaries. Patients recorded which of 4 categories (on, on with troubling dyskinesia, off, or asleep) best reflected their predominant functioning for the prior 30 minutes in half-hour intervals for 2 days.[15] Total time spent in each category was summed and averaged over 2 days to determine study eligibility. Patients were unaware of the 3-hour off time and/or on time with troubling dyskinesia per day eligibility requirement when completing the diaries.

Follow-up

Patients returned to their study site at 3 and 6 months for this phase of the study. The final follow-up visits for this phase of the study occurred in May 2006. Ten days prior to each visit, patients were mailed motor diaries to complete for 2 consecutive days prior to the visit.

Abbreviated motor function and quality-of-life assessments were conducted at 3 months. The entire baseline assessment was repeated at 6 months. Study neurologists and blinded neurologists independently assessed patients' UPDRS motor scores while patients were not taking medication. Patients receiving deep brain stimulation kept their stimulators on for the first assessment, then had them deactivated for return 1 hour later for assessment off medication, off stimulation. Patients receiving best medical therapy remained off medication and returned for a second assessment to equalize assessments in each group. After the second assessment, the deep brain stimulation systems were reactivated. All patients took their medications and returned 1 hour later for a third blinded and unblinded assessment. Patients completed the remaining assessments, including the UPDRS and neurocognitive tests, while taking medication.

Adverse events were collected and coded as to whether they were causally related to the study device, PD progression, PD medication, stimulation therapy, or surgical procedure. Each adverse event was recorded as being mild, moderate, or severe. Grading of the severity of the adverse event was decided by the site primary investigator. In post hoc analyses conducted to identify events due to early effects of surgery and stimulation adjustment, adverse events were divided into those that occurred within 3 months postenrollment and those occurring at 4 to 6 months. Some adverse events were further categorized as serious, defined as any event that was life-threatening, resulted in prolonged or new hospitalization, disability or congenital anomaly or birth defect, death, or required medical or surgical intervention to prevent 1 of the above outcomes.

Statistical Analysis

Analyses were based on the intent-to-treat principle. For patients with at least 1 follow-up visit but incomplete

follow-up, the last observation was carried forward and treated as the 6-month observation. For patients without baseline data, follow-up data, or both, the change score was set to zero. A second analysis excluded those without follow-up or baseline data. The primary outcome was the baseline to 6-month change in time spent in the on state without troubling dyskinesia. The mean group change was compared between treatment groups using a 2-sample *t* test. Secondary outcomes were measured as baseline to 6-month changes.

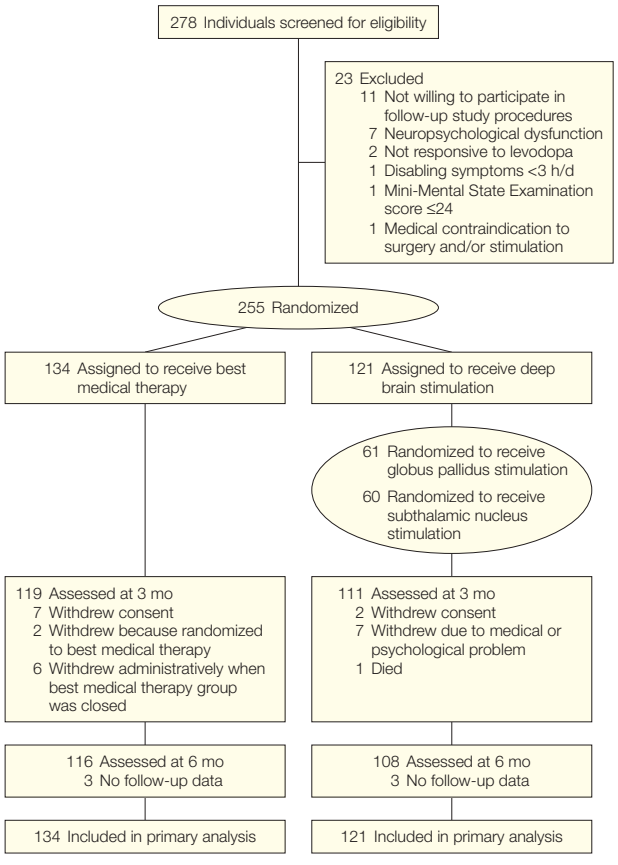
Medication usage was converted to levodopa equivalents for analysis.[17] An incidence risk ratio, the ratio of serious adverse event incidence rates per patient for deep brain stimulation compared with best medical therapy, was calculated. Statistical significance was based on the 95% confidence interval (CI) for the incidence risk ratio. Analyses were performed using SAS software version 9.1 (SAS Institute Inc, Cary, North Carolina). All statistical tests were 2-sided.

The sample size calculation was based on the primary outcome, which was the time spent in the on state without dyskinesia. The Cohen effect size was used to compare the difference in the average number of on hours between the best medical therapy group and the deep brain stimulation group.[18] All sample sizes and power calculations were 2-tailed with an α level of .05. The original sample size of 300 individuals permitted 99% and 93% power for detecting effect sizes of 0.5 and 0.4, respectively, in the primary outcome. The target sample size of 316 individuals included an anticipated 10% dropout in the best medical therapy group.

To recruit the target sample size needed for the phase 2 comparison of globus pallidus and subthalamic nucleus deep brain stimulation without further extending the study timeline, the data and safety monitoring board requested an interim analysis for efficacy on the first 214 patients. Results indicated that randomization to the best medical therapy group could be discontinued. The nominal significance level for the final analysis of the primary outcome was retrospectively set to .049.

Average differences in outcomes between best medical therapy and deep brain stimulation in the intent-to-treat group (n=255) were slightly smaller than those for the group with at least 1 follow-up visit (n=230). However, because results for the 2 analyses were similar, only the former is presented.

Figure. Patient Enrollment and Randomization Assignment



A score of 24 or less on the Mini-Mental State Examination is indicitive of cognitive impairment, which met the exclusion criteria for the study.

RESULTS

A total of 255 patients with PD were randomized to receive best medical therapy (n=134) or bilateral deep brain stimulation (n=121; of these patients, 61 were additionally randomized to globus pallidus and 60 to subthalamic nucleus) (FIGURE). Nineteen patients did not complete any follow-up assessments because they withdrew consent (9 in the deep brain stimulation group and 9 in the best medical therapy group), died (1 in the deep brain stimulation group), or were administratively withdrawn when the best medical therapy intervention group was closed (n=6). Baseline characteristics for patients with no follow-up did not differ from those who continued in the study except for mean age (67.6 years for noncompleters vs 62.0 years for completers; *P*=.01). Of the 255 patients included in the primary analysis, 211 completed 3-month evaluations and 224 completed 6-month evaluations.

Patients were male (82%), white (96%), and married (69%), had a mean (SD) age of 62.4 (8.9) years (range, 37-83 years), and it had been a mean (SD) of 12.4 (5.8) years since diagno-

sis of PD. One-quarter were aged 70 years or older. Overall, the baseline characteristics did not differ between the best medical therapy and deep brain stimulation groups (TABLE 1). However, the best medical therapy patients were treated with PD medications for a longer time (12.6 vs 10.8 years for deep brain stimulation patients; $P=.01$) and had a lower working memory index (97.3 vs 101.2, respectively; $P=.02$). Patients receiving best medical therapy and deep brain stimulation did not differ on either average hours per day in the on state without troublesome dyskinesia (7.0 vs 6.4 hours per day; $P=.07$), UPDRS score, or quality-of-life measures.

Motor Diary

Deep brain stimulation patients gained a mean of 4.6 hours per day of on time without troubling dyskinesia, while the mean change for the best medical therapy group was 0 hours (95% CI, 3.7-5.4, $P<.001$; TABLE 2). Off time decreased by 2.4 hours per day and on time with troubling dyskinesia by 2.6 hours per day in patients in the deep brain stimulation group compared with 0 and 0.3 hours per day in patients in the best medical therapy group ($P<.001$). Asleep time did not change significantly over time by group. Among those aged 70 years or older, patients receiving deep brain stimulation gained an average of 3.8 hours of on time per day, whereas patients receiving best medical therapy lost 0.5 hours per day ($P<.001$).

Motor Function

The change in off-medication UPDRS motor scores over 6 months was significantly greater in the deep brain stimulation group than in the best medical therapy group based on blinded-rater evaluations (in only 2% of cases did blinded raters believe they knew which intervention the patient received). Motor functioning improved (decreased) by 12.3 points in the deep brain stimulation group and by 1.7 points in the best medical therapy group while not taking medication ($P<.001$; TABLE 3). Similarly, in those aged 70 years or older, motor function improved 9.9 points in the deep brain stimulation group compared with 1 point in the best medical therapy group ($P<.001$). The UPDRS scores for activities of daily living and complications of therapy also improved signifi-

Table 1. Patient Baseline Characteristics by Treatment Group

	Best Medical Therapy (n = 134)	Deep Brain Stimulation (n = 121)	*P* Value
	No. (%)		
Age ≥70 y	37 (27.6)	31 (25.6)	.78
Men	110 (82.1)	98 (81.0)	.87
VA patient	80 (59.7)	73 (60.3)	>.99
White race	128 (95.5)	117 (96.7)	.75
Married	95 (70.9)	81 (66.9)	.50
Living with family	102 (76.1)	100 (82.6)	.37
Has personal caregiver help	60 (44.8)	56 (46.3)	.90
Family history of Parkinson disease	32 (23.9)	32 (26.4)	.67
	Mean (SD)		
Age, y	62.3 (9.0)	62.4 (8.8)	.97
Years taking Parkinson disease medications	12.6 (5.6)	10.8 (5.4)	.01
Not taking medication			
Hoehn and Yahr scale (range, 0-5)[a]	3.3 (0.8)	3.4 (0.9)	.85
Schwab and England scale (range, 0-100)[b]	51.0 (19.7)	50.4 (20.5)	.80
Unified Parkinson Disease Rating Scale score[a]			
I (mentation, behavior, and mood; range, 0-16)	2.7 (2.0)	2.6 (2.0)	.69
II (activities of daily living; range, 0-52)	19.7 (6.1)	19.1 (5.9)	.44
III (motor function while not taking medication, blinded assessment; range, 0-108)	43.2 (11.3)	43.0 (13.5)	.88
IV (complication of therapy; range, 0-23)	9.3 (3.1)	9.2 (3.0)	.79
On time, h/d			
Without troublesome dyskinesia	7.0 (2.9)	6.4 (2.7)	.07
Wth troublesome dyskinesia	4.2 (3.1)	4.4 (3.1)	.59
Parkinson Disease Questionnaire 39 score (range, 0-100)[a]			
Mobility	58.4 (21.4)	61.1 (21.0)	.30
Activities of daily living	54.8 (18.8)	55.0 (17.6)	.92
Emotional well-being	39.7 (18.6)	38.4 (19.3)	.57
Social support	26.0 (18.0)	26.9 (19.6)	.71
Beck Depression Inventory score (range, 0-63)[a]	11.7 (8.1)	11.3 (8.7)	.68
Mattis Dementia Rating Scale score (range, 0-144)[b]	136.6 (5.8)	136.7 (4.8)	.84
Processing Speed Index score (range, 54-150)[b,c]	89.4 (14.1)	91.0 (13.9)	.37
WAIS-III Working Memory Index score (range, 50-150)[b,d]	97.3 (13.6)	101.2 (13.3)	.02
Phonemic fluency[b,e]	44.7 (12.1)	45.7 (12.1)	.52
Category fluency (animal)[b,e]	49.5 (11.6)	50.9 (11.3)	.34
Hopkins Verbal Learning Test[b,e]			
Total (learning or memory)	39.9 (11.5)	38.9 (11.3)	.50
Delayed recall	38.1 (13.4)	37.3 (13.3)	.62
Finger tapping[b,e]	37.6 (12.9)	37.1 (11.4)	.75
Boston Naming Test (language)[b,e]	55.9 (4.3)	55.5 (4.5)	.44
WCST perseverative response[b,e]	43.7 (12.2)	46.1 (13.0)	.13
Stroop interference[b,e]	51.0 (7.6)	50.7 (7.4)	.71
Brief Visuospatial Memory Test[b,e]			
Delayed recall	42.4 (13.3)	42.1 (13.3)	.86
Total	39.7 (11.8)	39.0 (12.5)	.68

Abbreviations: VA, Veterans Affairs; WAIS-III, Wechsler Adult Intelligence Scales III; WCST, Wisconsin Card Sorting Test.
[a] Higher score indicates worse functioning.
[b] Higher score indicates better functioning.
[c] Indicates symbol search plus digit symbol.
[d] Indicates arithmetic plus letter-number plus digit span.
[e] These scales have a normal mean (SD) of 50 (10) and are T-scores.

Table 2. Patient Motor Diary Outcomes

Time	Best Medical Therapy (n = 134)			Deep Brain Stimulation (n = 121)			Best Medical Therapy Minus Deep Brain Stimulation	
	Baseline, Mean (SD)	6 mo, Mean (SD)	Mean Difference (95% CI)	Baseline, Mean (SD)	6 mo, Mean (SD)	Mean Difference (95% CI)	Mean Difference (95% CI)	*P* Value[a]
On, h/d[b]								
Without troublesome dyskinesia	7.0 (2.9)	7.1 (3.3)	0 (–0.5 to 0.5)	6.4 (2.7)	10.9 (4.2)	4.6 (3.8 to 5.3)	–4.5 (–5.4 to –3.7)	<.001
With troublesome dyskinesia	4.2 (3.1)	3.9 (3.3)	–0.3 (–0.8 to 0.3)	4.4 (3.1)	1.8 (3.0)	–2.6 (–3.3 to –2.0)	2.3 (1.5 to 3.2)	<.001
Off, h/d[b]	5.6 (2.9)	5.7 (2.8)	0 (–0.4 to 0.5)	5.9 (2.6)	3.4 (3.1)	–2.4 (–3.1 to –1.8)	2.5 (1.7 to 3.2)	<.001
Asleep, h/d	7.1 (1.7)	7.3 (2.0)	0.3 (0 to 0.6)	7.3 (1.8)	7.7 (2.0)	0.4 (0 to 0.7)	–0.1 (–0.6 to 0.4)	.66

Abbreviation: CI, confidence interval.
[a] Test for the change scores from baseline to 6 months between the best medical therapy group and the deep brain stimulation group.
[b] "On" and "off" time are described in the "Study Procedures" section of the "Methods."

cantly in the deep brain stimulation group compared with the best medical therapy group ($P<.001$ for all comparisons). When data were reexamined using a 5-point change in UPDRS motor score as a measure of a minimal clinically important change,[19] 71% of deep brain stimulation patients vs 32% of best medical therapy patients showed improvement in motor function at 6 months ($P<.001$), while 3% of deep brain stimulation patients and 21% of best medical therapy patients had clinically worsening scores ($P<.001$). Results were similar when only those aged 70 years or older were examined (61% of deep brain stimulation patients vs 27% of best medical therapy patients experiencing clinically improved motor function; $P<.006$). While the deep brain stimulation group had 9.0-second improvements in their stand-walk-sit test, patients in the best medical therapy group had worsening of their time by an average of 0.2 seconds from baseline ($P=.046$). Medication (in levodopa equivalents) decreased by 296 mg for patients in the deep brain stimulation group and increased by 15 mg over baseline for patients in the best medical therapy group ($P<.001$).

Quality of Life

Patients who received deep brain stimulation experienced significant improvements on the summary measure and on 7 of 8 Parkinson Disease Questionnaire 39 subscales compared with patients who received best medical therapy, who had little change from baseline on any subscale except stigma (Table 3). Social support scores did not change significantly as a result of intervention. Older patients receiving deep brain stimulation experienced significantly greater improvements in mobility, activities of daily living, and stigma subscales but did not differ in other subscales from older patients receiving best medical therapy (results not shown).

Neurocognitive Function

The deep brain stimulation and best medical therapy groups were generally well matched with regard to baseline neuropsychological test performance. However, the deep brain stimulation group performed significantly better ($P=.02$) on working memory at baseline. There were statistically significant treatment differences in the change between baseline and follow-up on composite measures of working memory ($P=.005$), processing speed ($P=.006$), phonemic fluency ($P<.001$), and delayed recall on the Brief Visuospatial Memory Test ($P=.03$; Table 3). Whereas the best medical therapy group showed slightly improved performance (1- to 2-point increases) at follow-up, patients in the deep brain stimulation group displayed mild decrements in performance (1.0- to 3.5-point decreases). Neither treatment was associated with significant change on the Mattis dementia or Beck depression scales or the majority of the measures assessing language, executive functioning, and learning and memory functioning.

Adverse Events

Deep brain stimulation patients reported 659 moderate or severe adverse events and best medical therapy patients reported 236 moderate or severe adverse events. The most frequent adverse events were falls, gait disturbance, dyskinesia, motor dysfunction, balance disorder, depression, and dystonia (≥9% patients for each). During the 6-month follow-up, there were significantly more events for the deep brain stimulation group than the best medical therapy group for falls ($P<.01$), gait disturbance ($P=.03$), depression ($P=.03$), and dystonia ($P<.01$). Surgical site infection (9.9%) and surgical site pain (9.0%) occurred only in the deep brain stimulation group. There was no study site variation in infection rates, ranging from 0 to 2 infections per site.

Most differences in adverse events between the 2 groups occurred in the first 3 months; only falls and dystonia were significantly greater for the deep brain stimulation group than for the best medical therapy group in the later 3

months (TABLE 4). The majority of adverse events (83%) in both groups had resolved by the 6-month follow-up.

Forty-nine deep brain stimulation patients (40%) experienced 82 serious adverse events. Sixty-eight serious adverse events (83%) were attributed to the surgical procedure, stimulation device, or stimulation therapy. Of the

Table 3. Outcomes at Baseline and 6 Months by Treatment Group[a]

Outcome	Best Medical Therapy (n = 134)			Deep Brain Stimulation (n = 121)			Best Medical Therapy Minus Deep Brain Stimulation	
	Baseline	6 mo	Mean Difference (95% CI)	Baseline	6 mo	Mean Difference (95% CI)	Mean Difference (95% CI)	*P* Value[b]
Not taking medication								
Hoehn and Yahr[c]	3.3 (0.8)	3.4 (0.9)	0 (–0.1 to 0.1)	3.4 (0.9)	2.8 (0.9)	–0.5 (–0.7 to –0.4)	0.5 (0.3 to 0.7)	<.001
Schwab and England[d]	51.0 (19.7)	49.3 (19.5)	–1.7 (–4.2 to 0.8)	50.4 (20.5)	66.2 (22.1)	15.8 (11.6 to 20.0)	–17.5 (–22.2 to –12.8)	<.001
Stand-walk-sit, s	36.3 (37.9)	36.9 (62.2)	–0.2 (–6.6 to 6.2)	34.6 (36.7)	25.2 (24.1)	–9.0 (–14.8 to –3.3)	8.8 (0.1 to 17.5)	.05
Unified Parkinson Disease Rating Scale score[c]								
I (mentation, behavior, and mood)	2.7 (2.0)	3.0 (2.1)	0.3 (–0.1 to 0.6)	2.6 (2.0)	2.6 (2.3)	0 (–0.4 to 0.4)	0.3 (–0.2 to 0.8)	.30
II (activities of daily living)	19.7 (6.1)	19.7 (5.9)	0 (–0.6 to 0.6)	19.1 (5.9)	14.5 (6.9)	–4.6 (–5.8 to –3.5)	4.6 (3.4 to 5.9)	<.001
III (motor function, blinded assessment when)								
Taking medication[e]	23.4 (11.1)	23.1 (11.7)	–0.4 (–1.9 to 1.2)	22.6 (12.6)	20.3 (11.3)	–2.4 (–4.0 to –0.8)	2.0 (–0.2 to 4.2)	.08
Not taking medication[f]	43.2 (11.3)	41.6 (12.7)	–1.7 (–3.3 to –0.1)	43.0 (13.5)	30.7 (14.5)	–12.3 (–14.3 to –10.3)	10.6 (8.1 to 13.2)	<.001
IV (complications of therapy)	9.3 (3.1)	8.8 (3.2)	–0.5 (–0.9 to 0)	9.2 (3.0)	5.8 (3.0)	–3.4 (–4.0 to –2.7)	2.9 (2.1 to 3.7)	<.001
Levodopa equivalents, mg[g]	1289 (546)	1303 (532)	15 (–44 to 73)	1281 (521)	985 (633)	–296 (–415 to –176)	310 (182 to 439)	<.001
Quality of Life								
Parkinson Disease Questionnaire 39 score[c]								
Mobility	58.4 (21.4)	58.0 (22.2)	–0.3 (–2.5 to 1.8)	61.1 (21.0)	48.8 (25.2)	–12.3 (–15.9 to –8.7)	12.0 (7.9 to 16.1)	<.001
Activities of daily living	54.8 (18.8)	56.3 (19.1)	1.5 (–0.6 to 3.7)	55.0 (17.6)	41.0 (22.2)	–14.0 (–17.1 to –11.0)	15.5 (11.9 to 19.2)	<.001
Emotional well-being	39.7 (18.6)	38.4 (18.5)	–1.3 (–3.7 to 1.1)	38.4 (19.3)	32.6 (19.5)	–5.7 (–8.6 to –2.8)	4.4 (0.7 to 8.2)	.02
Stigma	44.0 (24.5)	39.8 (25.5)	–4.2 (–7.1 to –1.2)	40.6 (24.3)	28.2 (23.7)	–12.5 (–16.4 to –8.6)	8.3 (3.6 to 13.1)	.001
Social support	26.0 (18.0)	27.5 (19.0)	1.5 (–1.7 to 4.6)	26.9 (19.6)	25.1 (21.1)	–1.7 (–5.1 to 1.7)	3.2 (–1.4 to 7.8)	.17
Cognition	42.2 (17.9)	43.8 (16.6)	1.7 (–1.0 to 4.3)	40.4 (17.8)	36.7 (20.4)	–3.7 (–6.8 to –0.5)	5.3 (1.3 to 9.4)	.01
Communication	45.2 (17.9)	47.8 (18.5)	2.6 (0.3 to 4.8)	45.3 (20.0)	42.6 (22.6)	–2.7 (–6.2 to 0.8)	5.2 (1.2 to 9.3)	.01
Bodily discomfort	47.6 (21.6)	48.6 (24.3)	1.1 (–2.0 to 4.1)	51.2 (21.2)	44.0 (21.1)	–7.2 (–10.5 to –4.0)	8.3 (3.8 to 12.7)	<.001
Single index	44.3 (13.1)	44.8 (13.4)	0.4 (–1.0 to 1.8)	44.9 (13.2)	37.3 (16.0)	–7.7 (–9.7 to –5.6)	8.1 (5.6 to 10.5)	<.001
Neurocognitive Tests								
Beck Depression Inventory score[c]	11.7 (8.1)	10.2 (6.9)	–1.5 (–2.6 to –0.3)	11.3 (8.7)	10.9 (8.6)	–0.4 (–1.7 to 0.9)	–1.0 (–2.7 to 0.6)	.22
Mattis Dementia Rating Scale total score[d]	136.6 (5.8)	137.5 (5.5)	0.9 (0.1 to 1.7)	136.7 (4.8)	136.6 (6.7)	–0.2 (–1.3 to 0.9)	1.1 (–0.3 to 2.4)	.12
Wechsler Adult Intelligence Scales III[d]								
Working memory index[h]	97.3 (13.6)	98.3 (14.9)	1.0 (–0.2 to 2.2)	101.2 (13.3)	99.6 (13.6)	–1.6 (–3.0 to –0.2)	2.6 (0.8 to 4.4)	.005
Processing speed index[i]	89.4 (14.1)	90.1 (13.9)	0.7 (–0.7 to 2.2)	91.0 (13.9)	88.4 (14.3)	–2.1 (–3.6 to –0.6)	2.9 (0.8 to 4.9)	.006

(continued)

Table 3. Outcomes at Baseline and 6 Months by Treatment Group[a] (continued)

Outcome	Best Medical Therapy (n = 134)			Deep Brain Stimulation (n = 121)			Best Medical Therapy Minus Deep Brain Stimulation	
	Baseline	6 mo	Mean Difference (95% CI)	Baseline	6 mo	Mean Difference (95% CI)	Mean Difference (95% CI)	*P* Value[b]
Neurocognitive Tests								
Phonemic fluency[d,j]	44.7 (12.1)	45.7 (11.8)	1.1 (–0.3 to 2.6)	45.7 (12.1)	42.2 (12.3)	–3.5 (–4.9 to –2.0)	4.6 (2.5 to 6.6)	<.001
Category (animal) fluency[d,j]	49.5 (11.6)	47.4 (11.9)	–2.0 (–4.0 to –0.1)	50.9 (11.3)	46.2 (11.3)	–4.7 (–6.6 to –2.7)	2.6 (–0.2 to 5.4)	.06
Boston Naming Test[d,j]	55.9 (4.3)	56.2 (4.0)	0.3 (0 to 0.6)	55.5 (4.5)	56.2 (3.8)	0.7 (0.3 to 1.1)	–0.4 (–0.8 to 0.1)	.13
Finger tapping[d,j]	37.6 (12.9)	38.7 (13.2)	1.0 (–0.7 to 2.7)	37.1 (11.4)	36.9 (11.3)	–0.2 (–2.1 to 1.6)	1.3 (–1.2 to 3.8)	.32
Stroop interference[d,j]	51.0 (7.6)	51.8 (8.4)	0.7 (–0.7 to 2.1)	50.7 (7.4)	49.8 (7.1)	–0.9 (–2.2 to 0.4)	1.6 (–0.4 to 3.5)	.11
WCST perseveration response[d,j]	43.7 (12.2)	45.0 (11.5)	1.3 (–0.9 to 3.4)	46.1 (13.0)	45.8 (12.6)	–0.3 (–2.4 to 1.7)	1.6 (–1.4 to 4.6)	.29
Hopkins Verbal Learning Test[d,j]								
Total (learning or memory)	39.9 (11.5)	40.2 (11.2)	0.3 (–1.3 to 2.0)	38.9 (11.3)	39.0 (11.3)	0 (–1.8 to 1.9)	0.3 (–2.2 to 2.7)	.82
Delayed recall	38.1 (13.4)	37.6 (13.4)	–0.5 (–2.4 to 1.4)	37.3 (13.3)	35.9 (12.9)	–1.4 (–3.1 to 0.4)	0.8 (–1.7 to 3.4)	.52
Brief Visuospatial Memory Test[d,j]								
Total	39.7 (11.8)	40.0 (12.4)	0.3 (–1.5 to 2.2)	39.0 (12.5)	38.3 (12.4)	–0.7 (–2.9 to 1.5)	1.1 (–1.7 to 3.9)	.45
Delayed recall	42.4 (13.3)	44.6 (13.7)	2.2 (0.2 to 4.1)	42.1 (13.3)	41.1 (13.6)	–1.0 (–3.1 to 1.0)	3.2 (0.4 to 6.0)	.03

Abbreviations: CI, confidence interval; WCST, Wisconsin Card Sorting Test.
[a] See Table 1 for the score range for each test. Values are expressed as mean (SD) unless otherwise indicated.
[b] Test for change scores from baseline to 6 mo between the best medical therapy group and the deep brain stimulation group.
[c] Higher score indicates worse functioning.
[d] Higher score indicates better functioning.
[e] Patient was taking medication (and receiving stimulation if in deep brain stimulation group); blinded assessment.
[f] Patient was not taking medication (and receiving stimulation if in deep brain stimulation group); blinded assessment.
[g] A dose of 100 mg of levodopa is equal to 125 mg of controlled-release levodopa is equal to 10 mg of bromocriptine is equal to 1 mg of pergolide is equal to 4 mg of ropinrirole is equal to 100 mg of amantadine is equal to 2 mg of trihexyphenidyl is equal to 10 mg of seligiline is equal to 2 mg of cogentin (based on expert opinion plus Pahwa et al[17]).
[h] Includes arithmetic plus letter-number plus digit span tests.
[i] Includes symbol search plus digit symbol tests.
[j] T-scores have a mean (SD) of 50 (10) and are T-scores.

39 serious adverse events related to the surgical procedure, 26 also were attributed to other concurrent causes. Two deep brain stimulation patients died; 1 death was secondary to cerebral hemorrhage that occurred 24 hours after lead implantation. The second death was due to lung cancer; however, the patient withdrew participation prior to deep brain stimulation implantation.

The most common serious adverse event was surgical site infection. Twelve patients had 16 infections related to the surgical procedure or device. These infections resulted in antibiotic therapy and removal of the leads, neurostimulator, or both. By the 6-month follow-up, some patients received implants again. Other serious adverse events included nervous system disorders (n=15), psychiatric disorders (n=11), device-related complications (such as lead migration and defective lead wire; n=8), cardiac disorders (n=4), other infections (n=2), and other events (n=20). Six patients experienced falls resulting in injury.

Fifteen best medical therapy patients (11%) experienced 19 serious adverse events. Events included nervous system (n=3), psychiatric (n=2), and cardiac (n=2) disorders; falls (n=2); other infections (n=2); and other events (n=8).

The overall incidence risk of experiencing a serious adverse event was 3.8 times higher (95% CI, 2.3-6.3) in deep brain stimulation patients than in best medical therapy patients. Serious adverse events were resolved in 99% of cases by 6 months. Although the serious adverse event rate was higher for deep brain stimulation patients than for best medical therapy patients, there was no difference in the serious adverse event rate between older (26%) and younger (25%) patients. Also, there were no differences in types of serious adverse events experienced by age (results not shown).

COMMENT

This large randomized controlled trial demonstrated that deep brain stimulation is superior to best medical therapy in improving motor function and quality of life in PD patients with motor complications and inadequate symptom control with medication, even

when older patients were included in the study. Most successful recent clinical trials of adjunctive medications for patients with PD and motor fluctuations report an improvement of on time of only 1 to 2 hours.[20-22] In the current study, patients receiving deep brain stimulation reported an average increase of 4.6 hours per day in on time, accompanied by reductions in on time with troubling dyskinesia and off time. Blinded UPDRS motor assessments, a unique feature of this study, confirmed self-reported improvements in motor functioning, which improved by 29% on average. This is comparable with improvements reported in several previous nonrandomized and unblinded studies of globus pallidus and subthalamic nucleus deep brain stimulation.[2] In contrast, most patients receiving best medical therapy did not show improvement in motor functioning after 6 months of management by movement disorder neurologists.

Improved motor functioning experienced by patients receiving deep brain stimulation was accompanied by significant improvements in quality of life. This finding is comparable with uncontrolled studies of deep brain stimulation of both subthalamic nucleus and globus pallidus, showing that patients who undergo deep brain stimulation experience improvements in quality of life.[23-25]

There were small but statistically significant group differences in change in cognitive test performance. While the best medical therapy group had slight improvements on several scales, deep brain stimulation was associated with small decrements in cognitive test performance. Previous studies of deep brain stimulation that included neuropsychological batteries have shown reductions in verbal associative fluency and other tasks following deep brain stimulation, interpreted by some as indications of executive dysfunction.[26,27] The present research reveals an overall similar pattern but also suggests that in the present cohort, several domains of executive functioning remain unaffected, whereas working memory and visuomotor speed reveal small deep brain stimulation effects. The specific factors contributing to these declines in information processing speed and working memory and their clinical significance remain to be explored.

The benefits of improved on time and quality of life need to be weighed against the risk of complications related to surgery. The number of adverse events was high in both groups, which was expected due to the method of ascertainment. However, adverse event rates were much higher in the deep brain stimulation group than in the best medical therapy group. Many adverse events experienced by patients in the deep brain stimulation group occurred during the first 3 months following surgery. Some reflect the typical consequences of surgery performed in older patients with comorbidities; others represent transient adverse effects associated with adjustments of stimulation and medication therapies during the postimplant period.

The most common neurobehavioral adverse events included depression, confusional state, and anxiety, which were all higher in patients in the deep brain stimulation group. A recent meta-analysis[28] of psychiatric events following deep brain stimulation reported that confusion accounted for 4% and depression for 2% of adverse events reported, which is comparable with our findings. Another review[29] of behavioral changes following subthalamic nucleus deep brain stimulation found that 41% of patients experienced cognitive problems and 8% experienced depression, indicating that behavioral issues can be a concern for treatment with deep brain stimulation.

Table 4. Most Frequent Moderate and Severe Adverse Events for Best Medical Therapy and Deep Brain Stimulation Groups[a]

	Adverse Events From Randomization to 3 Months					Adverse Events From 4 to 6 Months				
	Best Medical Therapy		Deep Brain Stimulation			Best Medical Therapy		Deep Brain Stimulation		
Adverse Events[b]	No. of Patients	No. of Events	No. of Patients	No. of Events	*P* Value[c]	No. of Patients	No. of Events	No. of Patients	No. of Events	*P* Value[c]
Fall	6	6	16	17	.02	5	5	14	14	.03
Gait disturbance	9	9	15	16	.14	4	4	10	10	.10
Dyskinesia	11	11	9	9	>.99	5	5	12	12	.08
Motor dysfunction	9	9	13	13	.27	6	6	3	3	.51
Balance disorder	6	6	12	13	.14	4	4	6	6	.53
Pain	3	3	10	13	.04	3	3	8	9	.12
Speech disorder	2	2	12	13	.004	3	3	7	7	.20
Dystonia	5	5	10	11	.18	1	1	8	8	.02
Headache	1	1	20	22	<.001	0	0	1	1	.48
Bradykinesia	4	4	12	13	.04	3	3	4	4	.71
Confusional state	1	1	13	15	<.001	3	3	3	3	>.99
Freezing phenomena	6	6	5	5	>.99	3	3	7	7	.20

[a] Adverse events exclude those that were rated as mild and those with low total frequency (<10 events); also note that adverse events include severe adverse events by definition.
[b] The total number of moderate and severe adverse events were 236 for the best medical therapy group and 659 for the deep brain stimulation group.
[c] Based on the number of unique patients.

There also were more falls in the deep brain stimulation group, often resulting in injuries (eg, fractures, dislocations, head trauma) requiring surgery or another intervention. Falls have not been reported specifically in most studies of deep brain stimulation. It is not clear whether deep brain stimulation increases fall risk directly or whether patients are at higher risk secondary to their improved function and greater activity level. These results suggest that clinicians treating movement disorders should review fall-risk precautions with their patients prior to administering deep brain stimulation.

Serious adverse events resulting in permanent sequelae were uncommon. One death was due to surgical complications following deep brain stimulation implantation. A second patient withdrew prior to deep brain stimulation and died due to lung cancer. Another patient required permanent institutionalization approximately 5 months after deep brain stimulation due to impaired activities of daily living and occasional delusions or hallucinations. Implant site infections occurred in approximately 10% of patients receiving deep brain stimulation.

These findings support and extend those of the study by Deuschl et al,[7] which involved 156 pairs of PD patients randomized to subthalamic nucleus deep brain stimulation or medical therapy. The Parkinson Disease Questionnaire 39, UPDRS, and motor diary findings were similar in both studies. Specifically, Deuschl et al[7] reported a 4.4-hour-per-day average gain in on time and in this study, we report a 4.6-hour-per-day average gain for patients in the deep brain stimulation group. Our results were comparable, even with the inclusion of a significant number of older patients. A larger proportion of patients in our study experienced serious adverse events than in the study by Deuschl et al[7] (25% vs 8%); there were 2 deaths in this trial and 4 in the study by Deuschl et al. The greater number of serious adverse events in our trial is likely attributable to inclusion of an older cohort of patients and the fact that the trial was rigorously monitored for identification of all adverse events.

A limitation of this study is that the subthalamic nucleus and globus pallidus cases are pooled into a single deep brain stimulation group. When the study was planned, it was thought that the differences at 6 months between those treated with subthalamic nucleus and those treated with globus pallidus would be small. Also, the second phase of the study comparing surgical targets remains blinded until completion of the study, which is anticipated to occur in April 2009. In a previous meta-analysis,[2] as well as a small randomized trial comparing subthalamic nucleus with globus pallidus,[30] there were no significant differences in motor outcomes by deep brain stimulation target, supporting our presumption of little or no difference by deep brain stimulation target group. Nonrandomized trials have identified more cognitive adverse events in patients who have undergone subthalamic nucleus than globus pallidus deep brain stimulation.[31] Phase 2 of this study, when completed, will provide an in-depth assessment of a wide variety of outcomes based on surgical target.

CONCLUSIONS

In this randomized controlled trial, deep brain stimulation was more effective than best medical therapy in alleviating disability in patients with moderate to severe PD with motor complications responsive to levodopa and no significant cognitive impairment. The extent of benefit was similar for younger and older patients, although adverse events were higher in older patients. The clinical significance of the adverse events and minor neurocognitive changes observed in patients in the deep brain stimulation group and, more importantly, whether patients who undergo deep brain stimulation view improvement in motor function and quality of life as outweighing adverse events, remain to be explored. More detailed analyses of adverse events and neurocognitive functioning following the conclusion of phase 2 of this study will shed light on these issues. Caution should be exercised, however, against overstating or understating the risks of deep brain stimulation for patients with PD. Physicians must continue to weigh the potential short-term and long-term risks with the benefits of deep brain stimulation in each patient.

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