ORIGINAL ARTICLE

Pallidal Deep-Brain Stimulation in Primary Generalized or Segmental Dystonia

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ABSTRACT

BACKGROUND

Neurostimulation of the internal globus pallidus has been shown to be effective in reducing symptoms of primary dystonia. We compared this surgical treatment with sham stimulation in a randomized, controlled clinical trial.

METHODS

Forty patients with primary segmental or generalized dystonia received an implanted device for deep-brain stimulation and were randomly assigned to receive either neurostimulation or sham stimulation for 3 months. The primary end point was the change from baseline to 3 months in the severity of symptoms, according to the movement subscore on the Burke–Fahn–Marsden Dystonia Rating Scale (range, 0 to 120, with higher scores indicating greater impairment). Two investigators who were unaware of treatment status assessed the severity of dystonia by reviewing videotaped sessions. Subsequently, all patients received open-label neurostimulation; blinded assessment was repeated after 6 months of active treatment.

RESULTS

Three months after randomization, the change from baseline in the mean (±SD) movement score was significantly greater in the neurostimulation group (–15.8±14.1 points) than in the sham-stimulation group (–1.4±3.8 points, P<0.001). During the open-label extension period, this improvement was sustained among patients originally assigned to the neurostimulation group, and patients in the sham-stimulation group had a similar benefit when they switched to active treatment. The combined analysis of the entire cohort after 6 months of neurostimulation revealed substantial improvement in all movement symptoms (except speech and swallowing), the level of disability, and quality of life, as compared with baseline scores. A total of 22 adverse events occurred in 19 patients, including 4 infections at the stimulator site and 1 lead dislodgment. The most frequent adverse event was dysarthria.

CONCLUSIONS

Bilateral pallidal neurostimulation for 3 months was more effective than sham stimulation in patients with primary generalized or segmental dystonia. (ClinicalTrials.gov number, NCT00142259.)

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P RIMARY DYSTONIA COMPRISES A GROUP of idiopathic, incurable movement disorders that vary with respect to age at onset, body distribution, and genetic association.[1] All these disorders are characterized by twisting, repetitive movements or abnormal postures caused by involuntary muscle contractions.[2] The mainstay of treatment for focal or segmental dystonia is the injection of botulinum toxin to denervate the affected muscles.[3] When this approach fails (because too many muscles are involved, the movement pattern is too complex, or neutralizing antibodies develop[4]), the management of dystonia becomes difficult. Drug therapy is often unsatisfactory,[5] which leaves many patients with a profound incapacity of movement and the related stigma. Therefore, surgical approaches that have a favorable risk–benefit ratio, such as deep-brain stimulation,[6] deserve investigation.

Reports on case series have described the highly successful use of continuous, high-frequency neurostimulation of the internal globus pallidus in severely disabled children[7,8] and adults[8-16] with primary generalized dystonia. There have been isolated case reports and small, uncontrolled cohort studies of the effect of this treatment on focal or segmental dystonia.[17-24] Recently, the French multicenter Stimulation du Pallidum Interne dans la Dystonie (SPIDY) study[10] reported prospective data with blinded assessments but did not include a control group.[25] Sham-controlled trials are of particular importance, given the well-known placebo effect in pharmacologic trials involving dystonia.[26] The placebo effect could be even greater with invasive therapies and could augment a possible rating bias by the treating physician. We report on the clinical efficacy and safety of bilateral pallidal deep-brain stimulation (delivered by means of permanently implanted brain electrodes connected through an extension to a fully implanted neurostimulator) for severe primary dystonia in a series of 40 patients who participated in a prospective trial of neurostimulation.

METHODS

STUDY DESIGN

We designed the study as a 3-month randomized, double-blind, sham-controlled trial, followed by either 3 or 6 months of open-label treatment, for a total of 6 months of neurostimulation in each group. During the study, we evaluated whether bilateral pallidal neurostimulation was effective in reducing symptoms of severe primary dystonia. The study was conducted at 10 academic centers in Germany, Norway, and Austria in collaboration with the Institute for Medical Informatics and Statistics at the University of Rostock, in Rostock, Germany. Data monitoring and management were performed by the Clinical Coordination Center in Marburg, Germany. A writing committee consisting of seven coauthors was responsible for analyzing and interpreting the data and writing the manuscript. The authors vouch for the completeness and veracity of the data and data analyses. The study sponsors were not involved in the design or execution of the trial, data analysis, or reporting of the trial results. The ethics committee of each participating center approved the study protocol, and all patients or their guardians provided written informed consent.

ELIGIBILITY

Eligible patients were between the ages of 14 and 75 years and had marked disability owing to primary generalized or segmental dystonia, despite optimal pharmacologic treatment, with a disease duration of at least 5 years. Exclusion criteria were previous brain surgery; cognitive impairment (<120 points on the Mattis Dementia Rating Scale, ranging from 0 to 144, with higher scores indicating higher functioning); moderate-to-severe depression (>25 points on the Beck Depression Inventory, ranging from 0 to 63, with higher scores indicating more severe depression); marked brain atrophy, as detected by magnetic resonance imaging (MRI) or computed tomography (CT); or other medical or psychiatric coexisting disorders that could increase the surgical risk or interfere with completion of the trial.

BASELINE MEASUREMENTS

Patients were videotaped with the use of a standardized protocol at baseline (within 6 weeks before surgery). Baseline measurements included ratings of movement and disability (as assessed by the Burke–Fahn–Marsden Dystonia Rating Scale,[27] with scores ranging from 0 to 120 and 0 to 30, respectively, and higher scores indicating greater impairment). Quality of life was assessed with the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36), which evaluates both physical and mental components of functioning on a scale of 0 to 100, with higher scores indicat-

ing a higher level of function.[28] The severity of dystonia and pain was assessed with the use of a visual analogue scale of pain and dystonia severity, with scores ranging from 0 to 10 and higher scores indicating greater severity. Measurements of walking (the duration and number of steps taken in a 14-m walk with one turn) and finger tapping (the number of taps in 30 seconds) were also performed. Cognitive and mental status were assessed with the Mattis Dementia Rating Scale (with scores ranging from 0 to 144 and lower scores indicating more severe dementia),[29] the Brief Psychiatric Rating Scale[30] (with scores ranging from 24 to 168 and higher scores indicating greater severity), the Beck Depression Inventory (with scores ranging from 0 to 63 and higher scores indicating more severe depression), and the Beck Anxiety Inventory[31] (with scores ranging from 0 to 63 and higher scores indicating more severe anxiety).

SURGICAL PROCEDURE

Permanent quadripolar electrodes (Medtronic model 3387 or 3389) were implanted bilaterally in the posteroventrolateral portion of the internal globus pallidus during one session, while the patient was under general anesthesia. The initial implantation target was 2 mm anterior to, 20 to 21 mm lateral to, and 2 to 6 mm below the midcommissural point; the localization of the site was further refined by a combination of direct visualization on MRI, microelectrode recordings, and intraoperative stimulation (depending on local resources). The electrodes were connected to a fully implanted neurostimulator (Kinetra, Medtronic) during the same or a subsequent surgical session. Postoperative MRI was performed in 24 patients to exclude asymptomatic hemorrhage and confirm adequate localization of electrodes at the ventral border of the posterolateral internal globus pallidus. In the remaining patients, target confirmation was obtained by postoperative stereotactic radiography or fusion of CT and MRI scans.

RANDOMIZATION AND TREATMENT

After surgery, patients were randomly assigned in a 1:1 ratio without stratification to receive either neurostimulation or sham stimulation with the use of a central randomization list. The numbers of patients in the two groups were balanced with the use of permuted blocks of four.

Within 1 week after surgery, a programming session was performed, during which the acute effects of increasing amplitudes of high-frequency neurostimulation were tested for each electrode contact (a trial of at least 30 seconds) in monopolar mode (frequency, 130 Hz; pulse width, 120 μsec). The contact for prolonged stimulation was selected on the basis of a reduction of dystonic hyperkinesia or the induction of phosphenes at a low threshold (suggesting proximity to the optic tract) or on the basis of neuroimaging studies (suggesting an electrode location at the ventral border of the pallidum in patients without acute stimulation effects). According to the group assignment, patients were either programmed to receive neurostimulation, with an amplitude of 0.5 V below the threshold of inducing acute adverse effects, or sham stimulation, with an amplitude of 0 V. Adjustments to measures of stimulation were not allowed during the first 3 months of the study unless intolerable adverse effects occurred. However, adjustments were performed at any time thereafter to maximize the clinical benefit or reduce adverse effects. Investigators adjusted doses of medication throughout the entire study as needed.

Patients were unaware of their group assignment until they had been reassessed at 3 months. Then the assignments were revealed, and neurostimulation was also initiated in the sham-stimulation group.

SERIAL MONITORING AND OUTCOME MEASURES

Patients were reassessed with the use of baseline instruments 3 months after randomization and after 6 months of active neurostimulation (i.e., 6 months after randomization in the neurostimulation group and 9 months after randomization in the sham-stimulation group). Two independent experts on dystonia, who were unaware of the group assignments and order of the examinations, rated the severity of dystonia while watching videos of the patients, with the use of the movement score on the Burke–Fahn–Marsden Dystonia Rating Scale.[27]

Safety was assessed according to the frequency and severity of spontaneously reported adverse events. Both new symptoms and a worsening of preexisting symptoms were classified as adverse events. Serious adverse events were defined as death, life-threatening illness, hospital admission or prolonged hospitalization, persistent disability, and an event requiring intervention to avoid any of these outcomes.

STATISTICAL ANALYSIS

The primary null hypothesis was an outcome of no significant difference in the change in the movement score (an average of the two scores recorded by observers who were unaware of the group assignments) from baseline to 3 months between patients receiving active neurostimulation and those receiving sham stimulation. We calculated that we would need a sample of 40 patients to provide the study with 90% power to detect a 25% difference between treatment groups while allowing for an overall dropout rate of 10%, with a 5% probability of a type I error on the basis of a two-sided Mann–Whitney test. Data from all patients who underwent randomization were analyzed; missing values were imputed with the last observation carried forward.

Secondary end points were the effect of neurostimulation on activities of daily living, the disability score on the Burke–Fahn–Marsden Dystonia Rating Scale, and quality of life (as assessed with the SF-36).[28] Exploratory end points were the rate of response (the number of patients with >25% improvement in the movement score on the Burke–Fahn–Marsden Dystonia Rating Scale), scores on the visual analogue scale for dystonia and pain, psychiatric scores (on the Beck Depression and Anxiety Inventories and the Brief Psychiatric Rating Scale), and chronometric tests of walking and tapping at 3 months.

Disease-related ratings after 6 months of active neurostimulation were compared with baseline ratings with the use of the Wilcoxon signed-rank test for matched pairs. All analyses of the secondary and exploratory outcomes were descriptive. The chi-square test was used for categorical data. All statistical tests were two-tailed and were not adjusted for multiple testing. No interim analysis was conducted. Statistical analyses were performed with the JMP statistical package, version 6.0 (SAS Institute).

RESULTS

Between August 2002 and May 2004, 60 patients with dystonic syndromes were referred to the participating centers for deep-brain stimulation. Forty entered the trial and were randomly assigned to the two study groups after surgery (Fig. 1). Their clinical characteristics are summarized in Table 1.
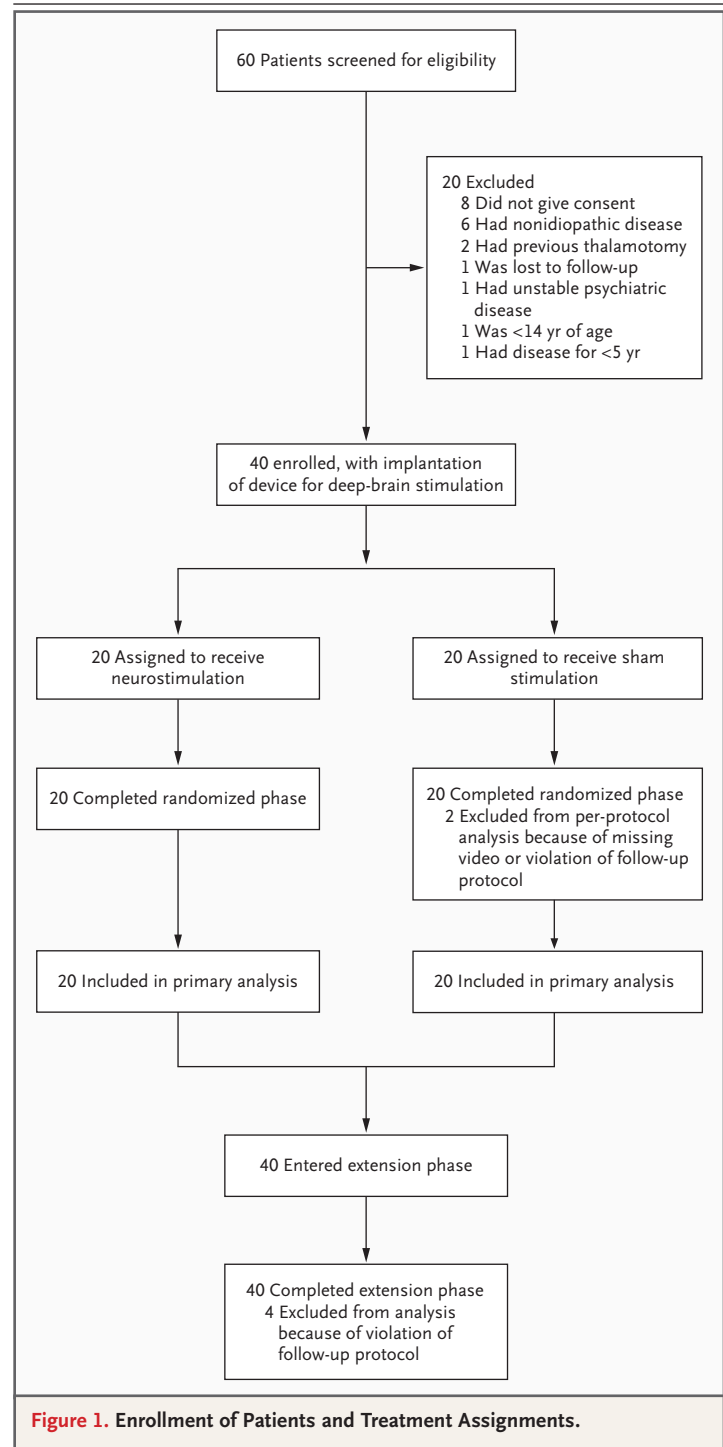
Sixteen patients had segmental dystonia, which

Figure 1. Enrollment of Patients and Treatment Assignments.

always affected the neck in combination with the face, shoulder, arm, or upper trunk. Patients with segmental dystonia, as compared with those with generalized dystonia, were older at the onset of disease (32.6±16.5 vs. 12.3±10.8 years, P<0.001)

and at the time of surgery (48.9±13.5 vs. 33.8± 10.1 years, P<0.001) and had a shorter duration of disease (16.3±7.1 vs. 21.9±7.9 years, P=0.05). The patients had previously taken multiple medications, which had been discontinued because of inefficacy or adverse effects. Thirty-five patients had received injections of botulinum toxin, but 21 patients had discontinued its use owing to an insufficient control of symptoms. The medications for dystonia that patients were taking at the time of surgery and that provided a partial but insufficient benefit are listed in Table 1.

Table 1. Characteristics of the Study Population.*

Characteristic	Neurostimulation (N=20)	Sham Stimulation (N=20)	P Value
Age — yr	40.5±13.5	38.4±13.8	0.88
Duration of disease — yr	21.8±8.1	17.2±7.5	0.08
Sex — no. (%)			
Male	13 (65)	14 (70)	0.74
Female	7 (35)	6 (30)	
Presence of *DYT1* mutation — no. (%)			
Positive	2 (10)	4 (20)	0.36
Negative	13 (65)	14 (70)	
Not available	5 (25)	2 (10)	
Distribution of dystonia — no. (%)			
Generalized	12 (60)	12 (60)	1.00
Segmental	8 (40)	8 (40)	
Dystonia treatment at study initiation — no. (%)			
Anticholinergics	6 (30)	3 (15)	0.26
Benzodiazepines	10 (50)	4 (20)	0.05
Antispastics	3 (15)	1 (5)	0.29
Neuroleptics	2 (10)	2 (10)	1.00
Tetrabenazine	3 (15)	2 (10)	0.63
Levodopa and dopa decarboxylase inhibitor	1 (5)	1 (5)	1.00
Intrathecal baclofen	1 (5)	1 (5)	1.00
Botulinum toxin within previous 4 mo	9 (45)	5 (25)	0.19
Stimulation measurements			
Amplitude — V			
At start of treatment	2.8±1.0	2.8±1.1	0.39
At 3 mo	3.2±0.9	NA	NA
At 6 mo	3.2±0.9	3.2±1.3	0.58
Pulse width — μsec			
At start of treatment	121.3±33.9	121.2±36.3	0.68
At 3 mo	122.2±37.5	NA	NA
At 6 mo	123.7±36.7	131.3±53.1	0.83
Frequency — Hz			
At start of treatment	136.5±16.1	135.9±14.4	0.13
At 3 mo	139.5±18.5	NA	NA
At 6 mo	135.7±37.5	132.8±28.5	0.88

* Plus–minus values are means ±SD. NA denotes not applicable.

RANDOMIZED STUDY PERIOD

Three months after randomization, severity scores were significantly lower in the neurostimulation group than in the sham-stimulation group (P<0.001) (Fig. 2A). The movement score improved by a mean of 15.8±14.1 points (a 39.3% reduction in symptoms) in the neurostimulation group, as compared with 1.6±4.0 points (a 4.9% reduction) in the sham-stimulation group (Table 2). In the neurostimulation group, 15 patients fulfilled our criterion of a positive response to treatment (>25% reduction in the movement score), as compared with only 3 patients in the sham-stimulation group.

Likewise, disability scores improved significantly in the neurostimulation group, by a mean of 3.9±2.9 points (a 37.5% reduction in disability), as compared with a mean of 0.8±1.2 points (8.3%) in the sham-stimulation group (Table 2). Neurostimulation was significantly superior on all symptom subscores of the Burke–Fahn–Marsden Dystonia Rating Scale and most of the disability items. Quality of life, as assessed on the basis of the score for the physical component of the SF-36, improved in the neurostimulation group by 10.1±7.4 points (a 29.8% improvement), which differed significantly from the change in the placebo group (3.8±8.4 points, an 11.4% improve-

ment). The effects on primary and secondary outcomes are summarized in Table 2.

OPEN-LABEL STUDY EXTENSION

Among the patients who had been randomly assigned to the sham-stimulation group during the first 3 months, the movement score on the Burke–Fahn–Marsden Dystonia Rating Scale improved by an average of 12.0±10.0 points (36.8%) after 6 months of continuous neurostimulation (Fig. 2B). Among patients originally assigned to receive neurostimulation, the movement score further improved, with a decline from 24.5±22.8 at 3 months to 19.8±15.1 at 6 months, but this additional improvement was not significant (P=0.24).

A comparison of the outcome measures at baseline and after 6 months of neurostimulation was used to assess the magnitude of the treatment effect in the entire study group (Table 3). All movement symptoms (except for speech and swallowing), all disability scores, the scores on the physical and mental components of the SF-36, and the global clinical assessments showed pronounced and significant improvements among patients in the neurostimulation group. The severity of dystonia as reflected by the movement score decreased by more than 75% in 5 patients, more than 50%
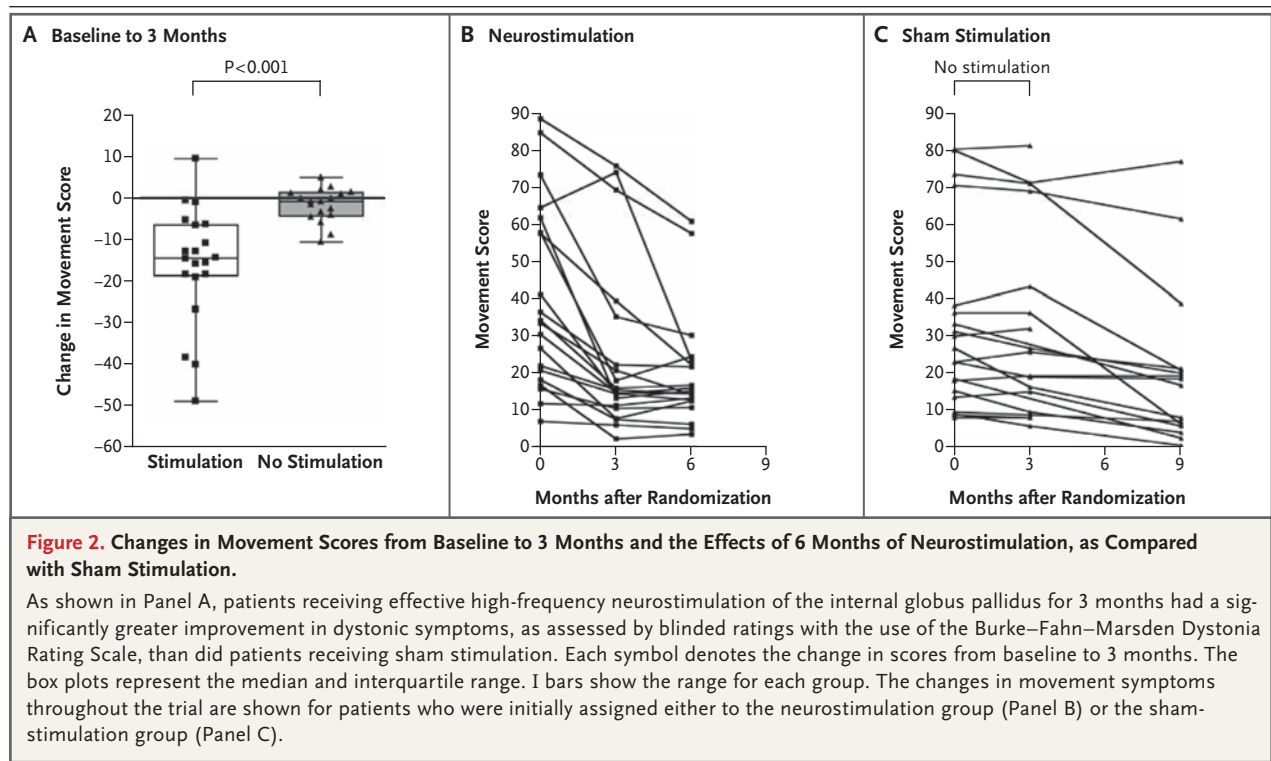

Figure 2. Changes in Movement Scores from Baseline to 3 Months and the Effects of 6 Months of Neurostimulation, as Compared with Sham Stimulation.

As shown in Panel A, patients receiving effective high-frequency neurostimulation of the internal globus pallidus for 3 months had a significantly greater improvement in dystonic symptoms, as assessed by blinded ratings with the use of the Burke–Fahn–Marsden Dystonia Rating Scale, than did patients receiving sham stimulation. Each symbol denotes the change in scores from baseline to 3 months. The box plots represent the median and interquartile range. I bars show the range for each group. The changes in movement symptoms throughout the trial are shown for patients who were initially assigned either to the neurostimulation group (Panel B) or the sham-stimulation group (Panel C).

Table 2. Results of the 3-Month Study Phase.*

Variable	Range of Possible Scores	Baseline				3 Months				Change from Baseline to 3 Months				
		Stimulation		Sham Stimulation		Stimulation		Sham Stimulation		Stimulation		Sham Stimulation		P Value
		no.	score	no.	score	no.	score	no.	score	no.	score	no.	score	
Burke–Fahn–Marsden Dystonia Rating Scale (Movement)†														
Total (with imputation)	0–120	20	40.2±24.9	20	32.6±24.3	20	24.5±22.8	20	31.1±24.0	20	−15.8±14.1	20	−1.4±3.8	<0.001
Total (without imputation)		20	40.2±24.9	20	32.6±24.3	20	24.5±22.8	18	31.7±25.2	20	−15.8±14.1	18	−1.6±4.0	
Face (eyes and mouth)	0–16	20	2.6±2.4	20	2.4±3.4	20	1.3±1.4	18	2.1±3.4	20	−1.3±1.7	18	0±0.4	0.004
Speech and swallowing	0–16	20	1.5±2.4	20	1.9±3.0	20	1.2±2.3	18	2.0±3.3	20	−0.4±0.5	18	0.1±0.4	0.002
Axial (neck and trunk)	0–24	20	12.8±5.8	20	10.2±4.6	20	7.9±5.3	18	9.4±4.4	20	−4.9±4.6	18	−0.9±1.8	<0.001
Arms and legs	0–64	20	23.3±18.5	20	18.1±17.2	20	14.1±17.0	18	18.1±18.3	20	−10.6±8.8	18	−2.3±4.6	<0.001
Burke–Fahn–Marsden Dystonia Rating Scale (Disability)														
Total	0–30	20	10.4±6.2	20	9.6±7.1	20	6.5±5.5	19	8.5±7.0	20	−3.9±2.9	19	−0.8±1.2	<0.001
Speech	0–4	20	1.5±1.3	20	1.6±1.4	20	1.0±1.3	19	1.5±1.4	20	−0.5±0.8	19	−0.1±0.2	0.04
Writing	0–4	20	1.8±1.0	20	1.5±1.1	20	1.3±0.7	19	1.4±1.1	20	−0.6±0.8	19	−0.1±0.6	0.04
Feeding	0–4	20	1.4±1.1	20	1.4±1.2	20	0.9±1.1	19	1.3±1.2	20	−0.6±8.2	19	−0.1±0.3	0.04
Eating and swallowing	0–4	20	0.8±1.0	20	0.8±1.1	20	0.4±0.6	19	0.7±1.0	20	−0.4±0.1	19	−0.1±0.7	0.32
Hygiene	0–4	20	1.3±1.1	20	1.2±1.3	20	0.6±1.1	19	0.9±1.2	20	−0.7±0.7	19	−0.2±0.4	0.01
Dressing	0–4	20	1.2±1.2	20	1.2±1.3	20	0.6±1.1	19	0.8±1.3	20	−0.6±0.6	19	−0.3±0.5	0.12
Walking	0–4	20	2.6±1.4	20	2.0±1.6	20	1.8±1.6	19	2.0±1.4	20	−0.8±0.9	19	−0.1±0.5	<0.001

	Range	N		N		N		N		N		N		P value
Visual-analogue scale‡															
Dystonia severity (patient's rating)	0–10	19	7.1±1.9	19	6.9±1.6	18	3.7±2.0	19	7.0±1.6	19	−3.4±2.1	18	0.1±1.5	<0.001
Pain severity (patient's rating)	0–10	19	4.6±2.9	19	4.8±2.4	18	1.7±1.7	19	4.8±2.5	19	−2.9±2.7	18	−0.1±1.0	<0.001
Dystonia severity (physician's rating)	0–10	19	6.8±2.2	20	6.4±1.9	19	3.8±2.1	19	6.5±1.8	19	−3.0±1.4	19	0.0±0.6	<0.001
Timed movement tests															
Finger tapping (counts)		20	228.4±175.0	18	230.4±173.6	19	221.9±169.1	19	256.8±183.8	19	−9.5±71.5	17	31.2±62.9	0.24
Cadence (steps/sec)		17	1.5±4.3	14	2.5±3.9	16	1.4±3.8	16	1.4±0.5	16	0±0.3	14	−1.0±3.9	0.87
Beck Depression Inventory‡	0–63	16	10.5±7.3	18	9.7±5.8	16	6.4±8.9	14	10.6±10.1	16	−5.1±8.4	16	−0.5±10.2	0.42
Beck Anxiety Inventory‡	0–63	18	13.7±11.0	19	12.1±10.5	17	8.0±6.5	16	10.5±7.4	19	−6.9±10.2	19	−2.4±11.4	0.10
Brief Psychiatric Rating Scale‡	24–168	19	27.0±7.3	19	27.8±8.0	19	21.4±4.6	18	24.8±5.5	18	−5.9±6.3	19	−3.0±8.4	0.09
SF-36§															
Physical component	0–100	17	33.9±9.0	17	33.5±6.6	18	44.1±9.0	17	37.7±10.3	17	10.1±7.4	16	3.8±8.4	0.02
Mental component	0–100	19	45.1±15.1	19	47.1±11.7	16	50.7±11.3	17	48.7±11.6	17	5.2±15.0	16	0.2±8.7	0.39

* Plus-minus values are means ±SD. The total movement score on the Burke–Fahn–Marsden Dystonia Rating Scale is the sum of individual scores for each body region and represents the severity of symptoms of dystonia. The individual score is based on the product of the severity factor (i.e., the clinical rating of the severity of dystonia, with 0 indicating no dystonia, and 4 maximal dystonia) and the provoking factor (i.e., the circumstances in which dystonia appears, with a score of 1 indicating that onset is task-specific, and a score of 4 that dystonia persists at rest). The scores for the eyes, mouth, and neck are "downweighted" by a factor of 0.5. The total disability score ranges from 0 to 30 and represents the sum of individual ratings for seven activities: speech (a score of 0 indicates the patient is easily understood, and a score of 4 indicates the presence of almost complete anarthria); handwriting (a score of 0 indicates legible handwriting, and a score of 4 indicates the inability to grasp a pen); the degree of dependence with respect to hygiene, dressing, and feeding (a score of 0 indicates normal ability, and a score of 4 complete dependence); swallowing (a score of 0 indicates normal ability, and a score of 4 indicates marked difficulty swallowing soft food and liquids); and walking (a score of 0 indicates normal ability, and a score of 6 indicates that the patient is confined to a wheelchair). For the primary outcome criterion (the movement score on the Burke–Fahn–Marsden Dystonia Rating Scale), all patients were included in the confirmatory analysis on the basis of the Mann–Whitney test, with missing values imputed according to the last-observation-carried-forward method. All statistical tests were two-tailed and were not adjusted for multiple testing.

† The value is the average score of the video-based ratings of two examiners who were unaware of the treatment assignment for each patient.

‡ A higher score on this scale indicates a greater severity of symptoms.

§ A higher score on this scale indicates a higher level of functioning.

Table 3. Results of the 6-Month Open-Label Extension Phase.*

Variable	Baseline		6 Months		Change from Baseline to 6 Months		
							P Value
	no.	score	no.	score	no.	score	
Burke–Fahn–Marsden Dystonia Rating Scale (Movement)							
Total	40	36.4±24.6	36	20.2±18.0	36	−16.7±13.0	<0.001
Face (eyes and mouth)	40	2.5±2.9	36	1.5±2.1	36	−0.8±1.5	<0.001
Speech and swallowing	40	1.7±2.9	36	1.3±2.2	36	−0.4±1.7	0.14
Axial (neck and trunk)	40	11.5±5.3	36	5.7±3.8	36	−6.1±4.6	<0.001
Arms and legs	40	20.7±17.8	36	11.6±14.2	36	−9.4±9.0	<0.001
Burke–Fahn–Marsden Dystonia Rating Scale (Disability)							
Total	40	10.0±6.6	36	5.9±5.6	36	−4.1±3.6	<0.001
Speech	40	1.5±1.3	36	1.1±1.2	36	−0.4±0.9	0.01
Writing	40	1.7±1.1	36	1.7±1.0	36	−0.4±0.8	0.003
Feeding	40	1.4±1.2	36	0.6±0.9	36	−0.7±0.9	<0.001
Eating and swallowing	40	0.8±1.0	36	0.4±0.6	36	−0.4±1.0	0.03
Hygiene	40	1.3±1.2	36	0.5±1.0	36	−0.7±0.6	<0.001
Dressing	40	1.2±1.2	36	0.5±1.0	36	−0.6±0.7	<0.001
Walking	40	2.3±1.5	36	1.4±1.5	36	−0.9±1.1	<0.001
Visual-analogue scale							
Dystonia severity (patient's rating)	38	7.0±1.7	34	3.6±2.2	34	−3.4±2.4	<0.001
Pain severity (patient's rating)	38	4.7±2.6	34	1.7±1.8	34	−2.8±2.9	<0.001
Dystonia severity (physician's rating)	39	6.6±2.0	35	3.4±1.9	35	−3.1±1.8	<0.001
Timed movement tests							
Finger tapping (counts)	38	229.3±172.0	33	254.8±164.0	33	36.3±111.5	0.05
Cadence (steps/sec)	31	1.9±2.7	28	1.7±0.5	27	0.1±0.5	0.48
Mattis Dementia Rating Scale†	34	136.3±16.2	31	137.5±17.8	31	1.5±5.8	0.23
Beck Depression Inventory	34	10.1±6.5	31	7.1±6.7	29	−3.1±5.7	0.008
Beck Anxiety Inventory	37	12.9±10.7	32	9.4±7.6	34	−3.5±10.5	0.09
Brief Psychiatric Rating Scale	38	27.4±7.6	33	25.3±7.1	33	−2.0±7.0	0.19
SF-36							
Physical component	36	33.7±7.7	34	44.1±9.1	34	10.6±9.9	<0.001
Mental component	36	46.2±13.2	34	51.8±11.8	34	4.0±12.9	0.01

* Plus–minus values are means ±SD. Significance of the comparisons was tested with the Wilcoxon test. All statistical tests were two-tailed and were not adjusted for multiple testing. For ranges of scales, see descriptions in Table 2.
† The scores on the Mattis Dementia Rating Scale range from 0 to 144, with lower scores indicating more severe dementia.

in 18 patients, and more than 25% in 30 patients. Six patients, including one who had the *DYT1* mutation in the torsin A gene, had a reduction in symptoms of 25% or less; treatment was considered to have failed in these patients. On average, the decline in the severity of movement symptoms did not differ significantly among 5 patients with primary generalized dystonia who had the *DYT1* mutation (−21.7±14.4) and 13 patients who did not have the mutation (−18.8±15.5) (P=0.80). A post hoc comparison of the relative decline in movement scores among the patients with general-

Table 4. Adverse Events.

Event	Neurostimulation		Sham Stimulation		Total
	Randomized Phase (stimulator on)	Extension Phase (stimulator on)	Randomized Phase (stimulator off)	Extension Phase (stimulator on)	
Serious adverse events — no. of events*					
Infection at the stimulator site	1	0	2	1	4
Lead dislodgment	1	0	0	0	1
Other adverse events — no. of events					
Postoperative confusion	1	0	0	0	1
Lead breakage	0	0	0	1	1
Seizure	1	0	0	0	1
Seroma	1	0	0	0	1
Dysarthria	1	1	0	3	5
Stuttering	0	1	0	0	1
Worsening of dystonia	0	1	0	1	2
Sleep disorder	0	0	0	1	1
Facial weakness	0	0	1	0	1
Gait disorder	0	1	0	0	1
Dysesthesias	0	1	0	1	2
Total events — no.	6	5	3	8	22
Total patients — no. (%)	5	4	3	7	19 (48)

* Serious events were those requiring admission to a hospital or prolonged hospitalization.

ized dystonia (a reduction of 41.9±26.5%) and those with segmental dystonia (a reduction of 52.6±23.6%) revealed no significant difference (P=0.41).

In the 20 patients receiving ongoing medical treatment for dystonia at enrollment, drug dosages were reduced by an average of 32.1% at 6 months; pharmacotherapy had been entirely discontinued in 5 of the patients. Stimulation measurements remained remarkably stable over time (Table 1).

Neurostimulation significantly decreased depression, as measured by the Beck Depression Inventory, but did not otherwise significantly alter mental or cognitive status (as measured by the Mattis Dementia Rating Scale, the Beck Anxiety Inventory, and the Brief Psychiatric Rating Scale) (Table 3).

ADVERSE EVENTS

During the initial 3-month randomized phase of the study, nine adverse events were reported in eight patients, of which six events occurred in the neurostimulation group and three in the sham-stimulation group (Table 4). Most of the events were well-known complications of the surgical procedure. Infection at the stimulator site, which occurred in three patients, was the most frequent source of perioperative complications, requiring the temporary removal of the implant in two patients. All adverse events during the randomized phase resolved without permanent sequelae.

During the open-label extension phase, 11 patients had a total of 13 adverse events (Table 4). Dysarthria (manifested as slurred but understandable speech), the most common event, occurred in five patients (12%). The adverse events during the extension phase were typically related to stimulation and resolved or improved by changing the stimulation measures. Dysarthria in one patient and dysesthesias in two patients persisted despite adjustments in neurostimulation and were accepted as permanent side effects because the best possible improvement of dystonia could not be achieved without the side effects. In one patient who had mild diabetes, a recurrent infection led to permanent removal of the neurostimulation system shortly after completion of the study.

DISCUSSION

In this 3-month, randomized trial with a sham control, we evaluated the effects of bilateral pallidal deep-brain stimulation for primary generalized and segmental dystonia. We found that 3 months of neurostimulation led to a reduction in the severity of dystonia as reflected by the movement score (a 39% improvement), a reduction in disability (38%), and an improvement in the physical aspects of the quality of life (30%); these improvements were significantly superior to those associated with sham stimulation. Patients who were initially assigned to the sham-stimulation group were switched to neurostimulation after 3 months, and similar benefits were observed across the entire study group after 6 months of continuous neurostimulation, with an average improvement in the movement score of 46%, as compared with baseline. Half the patients had more than a 50% reduction in symptoms. This symptomatic benefit translated into significant improvements in all activities of daily living, as assessed with the Burke–Fahn–Marsden Dystonia Rating Scale, and in significant improvement in the physical and mental dimensions of quality of life, as measured by the SF-36.

The benefits were evident despite the relatively short follow-up period. Previous studies have shown a delayed and progressive course of reduction in dystonia with pallidal neurostimulation. This divergence may reflect different clinical features of dystonia that were not adequately captured by current clinical rating scales. We saw first signs of improvement in mobile dystonia within hours to days after initiating effective neurostimulation, whereas fixed dystonic postures were more resistant and often continued to improve beyond the study period. Although a 6-month follow-up period may have been too short to assess the full range of improvement in all aspects of dystonia, our results closely match those of the only other prospective study on pallidal deep-brain stimulation for primary generalized dystonia, which reported an average 51% reduction in the movement score after 12 months.[10]

The clinical significance of the benefits of neurostimulation that we observed were greater than was the effect of high-dosage trihexyphenidyl, the most potent drug for the treatment of dystonia.[32] In this crossover trial for generalized dystonia, the average difference in scores on the Burke–Fahn–Marsden Dystonia Rating Scale between placebo and trihexyphenidyl was 6.9 points (25%), and only 19% of the patients had a reduction in scores of more than 50% with treatment.

Patients with generalized or segmental dystonia had a similar symptomatic benefit after 6 months of neurostimulation, which suggests that the two conditions are equally likely to respond favorably. Most important for the patients with segmental dystonia was the reduction of axial symptoms by an average of 50%, because cervical dystonia was the predominant clinical symptom in all cases. This observation may have important implications when one is considering neurostimulation for patients with focal cervical dystonia that is inadequately controlled by botulinum toxin.

Like other investigators,[16,33] we found a variable response to therapy among patients, but no single factor among the baseline variables predicted the magnitude of improvement. After 6 months of neurostimulation, 17% of patients had a poor response (defined as ≤25% improvement or a worsening of the condition), despite correct positioning of electrodes, as verified by postoperative neuroimaging. One of these patients had the *DYT1* mutation. The mean improvement among patients with generalized dystonia who had the *DYT1* mutation and among those who did not have the mutation was the same in the open-label extension phase (38% in each group) — a finding that does not corroborate a previous hypothesis that the presence of this mutation would increase the therapeutic benefit.[33] Such factors as the age at the time of the onset of disease, the duration of disease, and the distribution of dystonia were not related to the outcome.

We did not observe changes in cognitive status associated with bilateral pallidal deep-brain stimulation. In contrast to a recent report suggesting an increased risk of suicide after pallidal neurostimulation for dystonia,[34] mood actually improved significantly among the patients in our study, and we found no behavioral abnormalities. Device-related complications — including infections at the stimulator site, seroma, and lead dislodgment or breakage — amounted to 18% and were more frequent than previously reported for neurostimulation in Parkinson's disease.[35,36] One reason could be that the implant undergoes more mechanical stress in patients with dystonia, suggesting a need for an improvement in the device for patients with this condition.[10,37] None of our patients had in-

tracranial hemorrhage, but the assessment of such an infrequent surgical complication may require a larger series of patients. Neurologic adverse events related to high-frequency stimulation were not severe and usually resolved with adequate programming, except for mild dysarthria in one patient and mild dysesthesia in two patients.
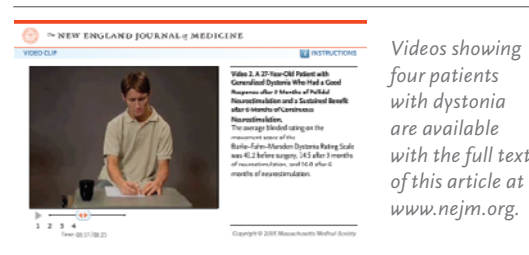
In conclusion, in this randomized comparison of the effects of neurostimulation and sham stimulation, we found that bilateral high-frequency stimulation of the internal globus pallidus is efficacious in the reduction of movement impairment and disability in patients with primary generalized or segmental dystonia. Extended follow-up studies are now needed to assess the long-term efficacy and safety of this treatment.

Videos showing four patients with dystonia are available with the full text of this article at www.nejm.org.

APPENDIX

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