ORIGINAL ARTICLE

A Randomized Trial of Deep-Brain Stimulation for Parkinson's Disease

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ABSTRACT

BACKGROUND

Neurostimulation of the subthalamic nucleus reduces levodopa-related motor complications in advanced Parkinson's disease. We compared this treatment plus medication with medical management.

METHODS

In this randomized-pairs trial, we enrolled 156 patients with advanced Parkinson's disease and severe motor symptoms. The primary end points were the changes from baseline to six months in the quality of life, as assessed by the Parkinson's Disease Questionnaire (PDQ-39), and the severity of symptoms without medication, according to the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III).

RESULTS

Pairwise comparisons showed that neurostimulation, as compared with medication alone, caused greater improvements from baseline to six months in the PDQ-39 (50 of 78 pairs, $P=0.02$) and the UPDRS-III (55 of 78, $P<0.001$), with mean improvements of 9.5 and 19.6 points, respectively. Neurostimulation resulted in improvements of 24 to 38 percent in the PDQ-39 subscales for mobility, activities of daily living, emotional well-being, stigma, and bodily discomfort. Serious adverse events were more common with neurostimulation than with medication alone (13 percent vs. 4 percent, $P<0.04$) and included a fatal intracerebral hemorrhage. The overall frequency of adverse events was higher in the medication group (64 percent vs. 50 percent, $P=0.08$).

CONCLUSIONS

In this six-month study of patients under 75 years of age with severe motor complications of Parkinson's disease, neurostimulation of the subthalamic nucleus was more effective than medical management alone. (ClinicalTrials.gov number, NCT00196911.)

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Parkinson's disease is one of the most disabling chronic neurologic diseases and leads to a significant loss of quality of life.[1,2] Several drugs are available that can effectively treat the symptoms of the disease, but long-term medical management is often complicated by the appearance of levodopa-induced motor complications, leading to rapid changes between periods of severe akinesia and periods of mobility that may be accompanied by troublesome hyperkinesias.[3] Dopamine agonists, amantadine, catechol *O*-methyltransferase (COMT) inhibitors,[3] and other drugs can effectively improve mobility and reduce dyskinesias initially but typically fail after several years.[4]

The administration of high-frequency continuous electrical stimulation to the subthalamic nucleus through a surgically implanted device has been shown to improve motor symptoms in patients with advanced stages of Parkinson's disease.[5,6] In open follow-up studies, mobility was significantly improved, and dyskinesias were dramatically reduced for up to five years.[7] However, this therapy will be acceptable to patients only if the symptomatic benefits are greater than the inherent surgical risks and reduce the burden of disease more effectively than optimal drug therapy. Parkinson's disease interferes with various aspects of the quality of life, particularly those related to physical and social functioning.[1,2] We performed a randomized, controlled trial comparing neurostimulation with the best medical management over a six-month period. Changes in the quality of life and motor function, the latter assessed while the patient was not receiving medication, were the primary outcome measures.

METHODS

PATIENTS

Patients were eligible for enrollment if they had received a clinical diagnosis of idiopathic Parkinson's disease according to the British Parkinson's Disease Society Brain Bank criteria[8] at least five years previously; were under 75 years of age; had parkinsonian motor symptoms or dyskinesias that limited their ability to perform the activities of daily living, despite receipt of optimal medical therapy; had no dementia or major psychiatric illness; and had no contraindications to surgery. Neurologists specializing in movement disorders at the participating centers gave their assurance that each patient had received state-of-the-art antiparkinsonian medication.[9]

STUDY DESIGN AND OUTCOMES

This study was an unblinded trial with a randomized-pairs design comparing deep-brain stimulation of the subthalamic nucleus with best medical management. The trial was conducted at 10 academic centers in Germany and Austria. The protocol was approved by the ethics committee at each participating center. All patients provided written informed consent.

The centers enrolled patients in pairs, with one patient randomly assigned to neurostimulation within six weeks after enrollment and the other to best medical treatment. Randomization, monitoring, and data management were performed by the Coordinating Center for Clinical Trials at Philipps University, Marburg, Germany. The primary end points were the changes from baseline to six months in the quality of life, as assessed by the Parkinson's Disease Questionnaire (PDQ-39) summary index,[10,11] and in the severity of motor symptoms while the patient was not taking medication, as assessed by the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III).[12] Scores for the PDQ-39 can range from 0 to 100, with higher scores indicating worse function. Scores for the UPDRS-III can range from 0 to 108, with higher scores indicating poorer condition. Patients were assessed after a 12-hour overnight withdrawal of antiparkinsonian medication and while they were taking medication, after the administration of a dose of liquid levodopa that was 50 percent higher than the usual morning dose of dopaminergic medication. When they are not taking medication, patients whose disease is severe enough to meet the criteria for inclusion in this trial are typically immobile, requiring help with the activities of daily living or being confined to bed or a wheelchair; however, the use of medication may not enable them to become completely mobile.

The secondary outcome measures included changes in a dyskinesia scale[13] and in the activities of daily living as assessed by the Unified Parkinson's Disease Rating Scale, part II (UPDRS-II), and the Schwab and England Scale,[12] with and without medication. Scores for the dyskinesia scale can range from 0 to 28, with higher scores indicating more severe dyskinesia. Scores for the UPDRS-II can range from 0 to 52, with higher scores indicating poorer function. Scores for the

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Schwab and England Scale can range from 0 to 100, with higher scores indicating better function. Motor symptoms (according to the UPDRS-III[12]) were also assessed while the patient was taking medication, as were cognitive function (according to the Mattis Dementia Rating Scale, for which scores can range from 0 to 144, with lower scores indicating more severe dementia[14]), neuropsychiatric function (according to the Montgomery and Asberg Depression Rating Scale[15] and the Brief Psychiatric Rating Scale,[16] for which scores can range from 0 to 60 and 18 to 126, respectively, and higher scores indicate more severe depression and poorer mental health, respectively), and the health-related quality of life (according to the Medical Outcomes Study 36-item Short-Form General Health Survey [SF-36] physical and mental summary scores, which are obtained by norm-based scoring, with higher scores indicating a better quality of life[17]).

Using diaries that separated the day into half-hour segments, the patients recorded their mobility during the three days before admission and for another three days six months after admission. They were trained to rate their condition as sleeping, immobile, neither fully mobile nor fully immobile, mobile without troublesome dyskinesias, or mobile with troublesome dyskinesias. The total number of hours spent in each of these categories was calculated, and the differences between the baseline and the six-month scores were compared between the groups. To compare the effects of changes in antiparkinsonian medications, we calculated that a 100-mg daily dose of standard levodopa was equivalent to the following doses of other medications: 133 mg of controlled-release levodopa; 75 mg of levodopa plus entacapone; 1 mg of pergolide, pramipexole, lisuride, or cabergoline; 5 mg of ropinirole; 10 mg of bromocriptine or apomorphine; and 20 mg of dihydroergocriptine.

Safety was assessed by recording the frequency and severity of reported adverse events. Any new symptom or worsening of a preexisting symptom was classified as an adverse event.

INTERVENTIONS

Patients assigned to neurostimulation underwent bilateral stereotactic surgery under local anesthesia. The subthalamic nucleus was targeted by means of stereotactic magnetic resonance imaging, ventriculography, microelectrode recording, or a combination of these techniques; the techniques used varied among the centers according to the institutional surgical protocols. The anatomical target coordinates were confirmed to be 0 to 3 mm behind the midcommisural point, 4 to 6 mm below the intercommisural line, and 11 to 13 mm lateral to the midplane of the third ventricle. The final implantation point was the position at which the most pronounced effect on rigidity and other symptoms of Parkinson's disease was obtained at the lowest stimulation intensity and with the largest safety margin (as determined by the difference in the intensity of stimulation between the clinical effect and the occurrence of unwanted effects) during intraoperative testing. The permanent electrode (model 3389 DBS, Medtronic) and the pulse generator (Kinetra, Medtronic) were implanted, and the final position of the electrode was confirmed by neuroimaging. Postoperatively, the optimal stimulation settings and antiparkinsonian medication were progressively adjusted according to the patient's response. The standard pulse setting was 60 μsec in duration at 130 Hz, with voltage adjusted to the individual patient.

Patients assigned to medical treatment received individualized optimal drug therapy according to the guidelines of the German Society of Neurology.[9] The drugs were adjusted according to the patient's needs throughout the study.

STATISTICAL ANALYSIS

On the basis of earlier treatment results,[18] we determined that 77 patients would need to be enrolled in each treatment group to detect a mean difference of 0.5 SD (using a two-sided test with an α value of 0.05 and a β value of 0.2, and assuming a dropout rate of 20 percent) between the groups. Primary outcome analysis was conducted according to the intention-to-treat principle. The primary outcome variables were the changes in a patient's scores from baseline to six months. For each primary end point, we subtracted the change in scores for the partner treated with medication from the change in scores for the partner treated with neurostimulation and tested the significance of the pairwise differences using the sign test. The nominal significance level for the final analysis was set to 0.04806 (two-sided), with adjustment for a planned interim analysis after follow-up of the first 38 pairs at a nominal α level of 0.005.[19] In the confirmatory analysis, missing follow-up values for the PDQ-39 summary index and the UPDRS-III scores while the patient was not taking medication were imputed to be the highest (worst) score for the

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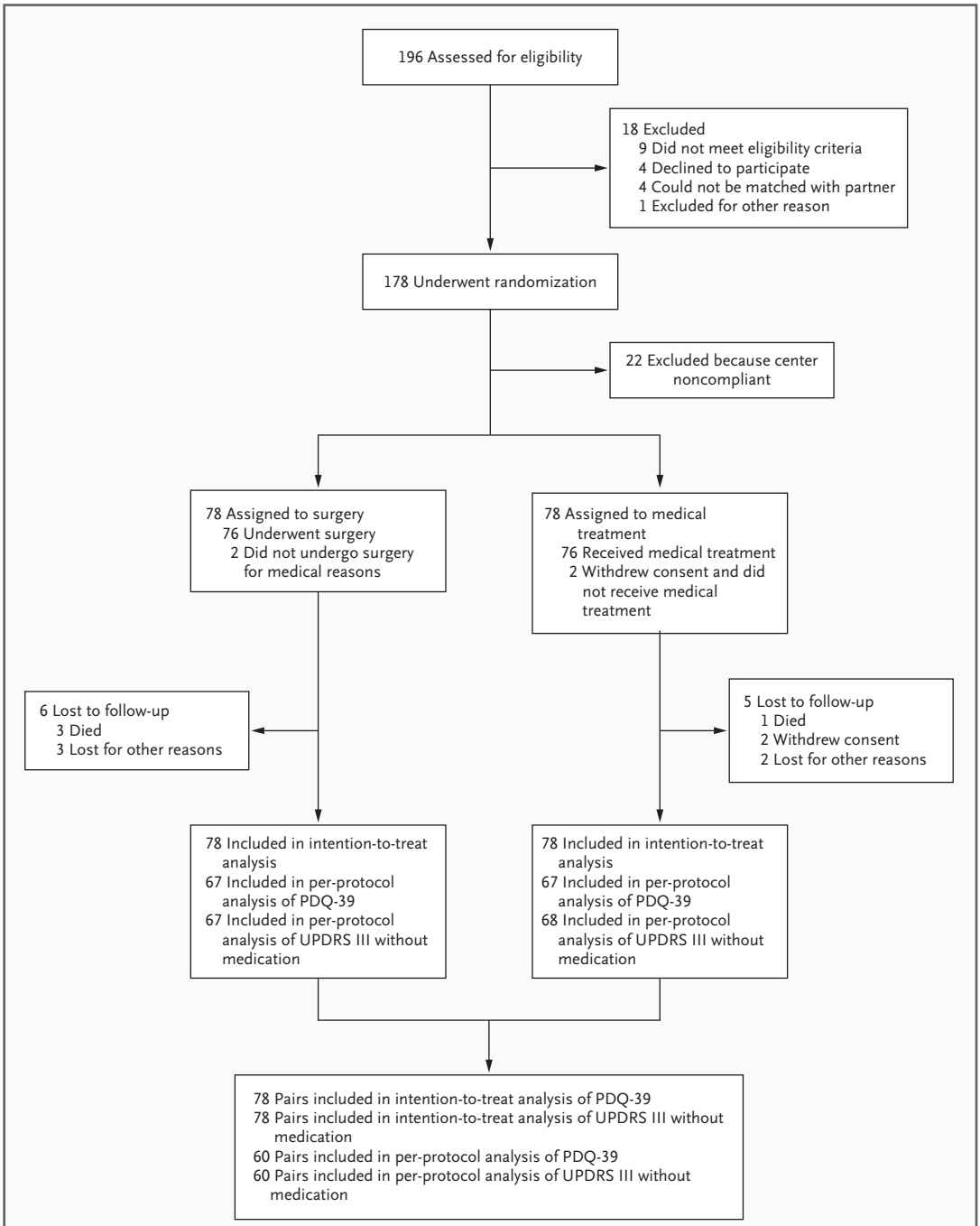

Figure 1. Enrollment and Outcomes.

PDQ-39 denotes the Parkinson's Disease Questionnaire, and UPDRS-III the Unified Parkinson's Disease Rating Scale, part III.

neurostimulation group and the lowest (best) score for the medication group. This is a strictly conservative analytic strategy. The study outcome was considered to be positive only if the neurostimulation group had significantly better results for both primary end points than the medication group.

The secondary outcome values were the changes from baseline to six months in scales that measured the severity of the disease. All analyses of

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Neurostimulation (N=78)	Medical Treatment (N=78)
Age — yr	60.5±7.4	60.8±7.8
Duration of levodopa treatment — yr†	13.0±5.8	13.8±5.6
Dose of levodopa or equivalent — mg/day	1176±517	1175±461
Male sex — no. (%)	50 (64)	50 (64)
Hoehn and Yahr stage, without medication — no. (%)‡		
1.0, unilateral disease	0	0
1.5, unilateral disease with axial involvement	0	2 (3)
2.0, mild bilateral disease without balance problems	1 (1)	2 (3)
2.5, mild bilateral disease with balance problems	10 (13)	6 (8)
3.0, mild-to-moderate bilateral disease, balance problems, independent in daily activities	17 (22)	13 (17)
4.0, severe disability, able to walk and stand with some assistance	40 (51)	41 (53)
5.0, wheelchair-bound or bedridden	10 (13)	14 (18)

* Plus–minus values are means ±SD. There were no significant differences between groups.
† Values are based on 75 patients in the neurostimulation group and 73 patients in the medical-treatment group.
‡ The Hoehn and Yahr stage has been described in detail elsewhere.[20]

the secondary outcomes were descriptive. To address problems arising from missing values, the Wilcoxon–Mann–Whitney test for independent samples was applied, despite the pairwise data structure. The chi-square test was used for categorical data. Statistical analyses were performed with the SAS statistical package, version 8.02.

RESULTS

STUDY POPULATION

Of 196 patients who were screened between 2001 and 2004, 178 were randomly assigned to neurostimulation or best medical treatment (Fig. 1). Twenty-two patients at one center were excluded from the analysis because the patients assigned to medical treatment were advised to return for immediate surgery in case of insufficient improvement. The center was closed after consultation with the monitoring committee. The treatment results among these excluded patients did not differ significantly from those in the intention-to-treat population; the excluded patients were not included in the analysis of adverse events. The intention-to-treat population thus consisted of 78 pairs of patients (156 patients) who were successfully randomly assigned to treatment. There were no significant differences in important baseline characteristics between the two treatment groups (Table 1).

EFFICACY

According to the intention-to-treat analysis of the 78 pairs of patients, in 50 pairs, the patient treated with neurostimulation had greater improvement in the score on the PDQ-39 summary index than did the patient assigned to medical treatment ($P=0.02$), and in 55 pairs, the patient treated with neurostimulation had greater improvement in the score on the UPDRS-III administered when the patients were not taking medication ($P<0.001$) (Table 2). This favorable result was obtained despite rigid criteria for the replacement of missing data that gave an advantage to medical treatment in the results. Therefore, neurostimulation was considered superior to medical treatment.

The mean PDQ-39 summary index score was 41.8±13.9 at baseline and 31.8±16.3 at six months in the neurostimulation group, as compared with 39.6±16.0 and 40.2±14.4, respectively, in the medication group (Table 3). This result corresponds to an improvement of about 25 percent in the neurostimulation group as compared with practically no change in the medication group. Treatment with

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Table 2. Paired Analysis of Primary Outcome Measures.*

Primary Outcome Measure	Pairs of Patients	Outcome Favored Neurostimulation	Outcome Favored Medical Treatment	Tied	P Value†
		no. of pairs (%)			
PDQ-39 summary index					
Intention-to-treat population					
Total no.	78	50 (64)	28 (36)	0	0.02
6-Mo data missing		1	9		
Per-protocol population	60	45 (75)	15 (25)	0	<0.001
UPDRS-III, without medication					
Intention-to-treat population					
Total no.	78	55 (71)	21 (27)	2 (3)	<0.001
6-Mo data missing		0	12		
Per-protocol population	60	51 (85)	8 (13)	1 (2)	<0.001

* The number of pairs of patients is shown according to whether the outcome was better for the partner receiving neurostimulation or the partner receiving medical treatment. When a value was missing for the partner receiving neurostimulation, it was replaced by the worst possible value. When a value was missing for the partner receiving medical treatment, it was replaced by the best possible value.
† P values were calculated by the sign test.

neurostimulation resulted in a 22 percent improvement in the physical summary score of the SF-36, a generic quality-of-life scale (Table 3). We performed a secondary sensitivity analysis of the findings for the primary outcome criteria on a per-protocol basis; this analysis also showed that the outcome was better among patients treated with neurostimulation than among those who received medical treatment: in 45 of 60 pairs, the patient treated with neurostimulation had greater improvement in the score on the PDQ-39 summary index than the patient who received medical treatment (P<0.001) and in 51 of 60 pairs, the patient treated with neurostimulation had greater improvement in the UPDRS-III score (P<0.001).

Individual domains of the PDQ-39 were affected differently by treatment (Fig. 2A). Improvements of 24 to 38 percent were obtained for mobility, activities of daily living, emotional well-being, stigma, and bodily discomfort. In contrast, there was no improvement in social support, cognition, or communication. The greatest improvement occurred in activities of daily living, a result consistent with the significant improvement in other secondary outcome values that measure the extent of impairment in daily life (the UPDRS-II and the Schwab and England Scale).

The effect of neurostimulation on motor symptoms was assessed with the use of the UPDRS-III while the patient was not taking medication. The mean score improved from 48.0±12.3 at baseline to 28.3±14.7 at six months in the neurostimulation group, an improvement of 41 percent, but remained unchanged in the medication group (46.8±12.1 at baseline and 46.0±12.6 at six months). The UPDRS-III score obtained while the patient was taking medication improved in the neurostimulation group from 18.9±9.3 at baseline to 14.6±8.5 at six months but remained unchanged in the medication group (17.3±9.6 at baseline and 17.5±10.6 at six months).

The secondary outcome measures were selected to identify additional disease dimensions that are improved with treatment. Activities of daily living while the patient was not taking medication, as assessed by the UPDRS-II, markedly improved (by 39 percent) in the neurostimulation group and slightly worsened (by 5 percent) in the medication group. A small difference in favor of neurostimulation was also observed in this scale when the patients were taking medication. Impairment, as measured by the Schwab and England Scale with and without medication, improved in the neurostimulation group and worsened in the medication group. Emotional and cognitive measures did not differ significantly between the neurostimu-

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Table 3. Changes in Primary and Secondary End Points from Baseline to Six Months.*

End Point	Baseline				6 Mo				Change from Baseline to 6 Mo				P Value
	Neurostimulation Group		Medication Group		Neurostimulation Group		Medication Group		Neurostimulation Group		Medication Group		
	no. of patients	*mean ±SD*	*no. of patients*	*mean ±SD*	*no. of patients*	*mean ±SD*	*no. of patients*	*mean ±SD*	*no. of patients*	*mean ±SD (95% CI)*	*no. of patients*	*mean ±SD (95% CI)*	
PDQ-39 summary index	78	41.8±13.9	78	39.6±16.0	71	31.8±16.3	73	40.2±14.4	71	9.5±15.3 (5.9 to 13.1)	73	–0.2±11.2 (–2.9 to 2.4)	0.02†
UPDRS-III, without medication	78	48.0±12.3	78	46.8±12.1	71	28.3±14.7	72	46.0±12.6	71	19.6±15.1 (16.1 to 23.2)	72	0.4±9.5 (–1.8 to 2.6)	<0.001†
PDQ-39 subscales													
Mobility	78	62.0±22.3	78	59.5±23.5	71	46.8±28.0	73	60.4±22.5	71	14.8±27.7 (8.2 to 21.3)	73	–0.8±19.6 (–5.3 to 3.8)	<0.001
Activities of daily living	78	55.0±23.6	78	50.5±22.1	71	33.3±24.4	73	52.4±21.3	71	20.7±26.1 (14.5 to 26.9)	73	–2.0±17.9 (–6.2 to 2.2)	<0.001
Emotional well-being	78	43.8±21.0	78	39.4±21.8	71	32.1±19.6	73	40.7±21.3	71	11.5±23.7 (5.9 to 17.1)	73	–0.8±16.8 (–4.7 to 3.2)	<0.001
Stigma	78	33.5±23.0	78	30.5±22.9	71	22.0±23.1	73	31.1±22.7	71	11.1±22.4 (5.9 to 16.3)	73	–0.1±17.6 (–4.3 to 4.0)	<0.001
Social support	78	20.7±20.8	78	24.0±21.1	71	17.8±20.6	73	24.5±22.5	71	2.3±21.8 (–2.9 to 7.5)	73	0.3±20.2 (–4.4 to 5.0)	0.60
Cognition	78	33.5±18.7	78	32.6±19.3	71	31.9±19.3	73	33.4±16.7	71	1.8±18.1 (–2.5 to 6.1)	73	–0.5±16.1 (–4.3 to 3.2)	0.44
Communication	78	37.6±19.8	78	32.4±21.1	71	34.2±24.0	73	34.0±19.1	71	2.6±22.1 (–2.6 to 7.8)	73	–1.1±17.4 (–5.2 to 2.9)	0.25
Bodily discomfort	78	48.0±22.2	78	48.3±23.6	71	36.7±22.7	72	45.8±21.9	71	11.3±26.4 (5.1 to 17.6)	72	3.1±18.1 (–1.2 to 7.3)	0.009
SF-36													
Physical	73	29.9±7.8	73	31.1±8.4	64	36.6±10.2	66	30.4±7.7	60	–6.4±8.0 (–8.4 to –4.3)	63	0.5±7.5 (–1.4 to 2.3)	<0.001
Mental	73	42.1±10.4	73	42.6±10.1	64	45.1±11.1	66	42.3±11.0	60	–2.4±12.3 (–5.6 to 0.7)	63	0.3±9.4 (–2.0 to 2.7)	0.04

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UPDRS-III, with medication	78	18.9±9.3	78	17.3±9.6	71	14.6±8.5	73	17.5±10.6	71	4.0±10.1 (1.7 to 6.4)	73	–0.4±7.7 (–2.2 to 1.4)	0.01
UPDRS-II, without medication	78	22.5±7.2	78	21.9±6.4	72	13.7±7.9	72	22.9±5.7	72	8.8±8.6 (6.8 to 10.8)	72	–0.8±6.4 (–2.3 to 0.7)	<0.001
UPDRS-II, with medication	78	9.0±5.5	78	7.9±5.8	72	7.6±5.4	73	9.0±5.3	72	1.5±5.4 (0.2 to 2.7)	73	–1.1±5.2 (–2.3 to 0.1)	0.005
Dyskinesia scale													
Without medication	78	0.5±2.0	78	0.5±1.7	71	0.2±1.7	71	0.1±0.6	71	0.2±2.2 (–0.4 to 0.7)	71	0.2±1.7 (–0.2 to 0.6)	0.78
With medication	78	6.7±5.3	78	8.4±5.9	70	3.1±3.5	71	8.6±5.5	70	3.4±4.5 (2.3 to 4.5)	71	–0.4±4.6 (–1.5 to –0.7)	<0.001
Schwab and England Scale													
Without medication	78	47±19	78	48±19	71	70±20	72	45±18	71	–23±22 (–28 to –18)	72	1±16 (–2 to 5)	<0.001
With medication	78	80±19	78	82±17	71	83±16	72	79±15	71	–4±16 (–7 to 0)	72	3±16 (0 to 7)	0.02
Levodopa or equivalent dose (mg/day)	78	1176±517	78	1175±461	71	597±381	71	1060±467	71	–593±548 (463 to 722)	71	–95±390 (3 to 187)	<0.001
Mattis Dementia Rating Scale	78	139.6±3.8	77	140.3±3.4	68	137.5±5.7	67	139.6±4.7	68	2.0±4.9 (0.8 to 3.2)	67	0.5±4.0 (–0.5 to 1.5)	0.14
Montgomery and Asberg Depression Rating Scale	78	8.5±5.5	78	7.7±5.8	65	8.1±6.6	69	8.5±5.4	65	0.3±7.2 (–1.5 to 2.1)	69	–0.6±6.3 (–2.1 to 0.9)	0.31
Brief Psychiatric Rating Scale	75	27.7±5.2	73	27.1±6.2	65	24.8±5.3	69	26.4±5.3	65	2.7±6.9 (1.0 to 4.4)	68	0.8±6.2 (–0.7 to 2.3)	0.13

* The Wilcoxon–Mann–Whitney test was used to determine unadjusted two-sided P values for all comparisons except those involving the two primary outcome criteria (PDQ-39 summary index and the UPDRS-III without medication). CI denotes confidence interval. Scores for the PDQ-39 can range from 0 to 100. Unless otherwise noted, scores for the UPDRS-II can range from 0 to 52, and scores for the UPDRS-III can range from 0 to 108. Scores for the dyskinesia scale can range from 0 to 28.[13] Scores for the Mattis Dementia Rating Scale can range from 0 to 144. Scores for the Montgomery and Asberg Depression Rating Scale can range from 0 to 60. Scores for the Brief Psychiatric Rating Scale can range from 18 to 126. The SF-36 physical and mental summary scores are obtained by norm-based scoring, with a mean of 50 and a standard deviation of 10. Scores for the Schwab and England Scale can range from 0 to 100. For the SF-36, the Schwab and England Scale, and the Mattis Dementia Rating Scale, higher scores indicate better function or quality of life. For all other scales, lower scores indicate better function or quality of life.

† For the PDQ-39 summary index and the UPDRS-III without medication, all patients randomly assigned to treatment were included in the confirmatory analysis (with the unadjusted two-sided sign test used to determine the pairwise differences between the changes, as shown in Table 2). When a value was missing for the partner receiving neurostimulation, it was replaced by the worst possible value, and when a value was missing for the partner receiving medical treatment, it was replaced by the best possible value. However, mean (±SD) values were calculated from available data only, without replacement of missing values, which accounts for the varying numbers of patients.

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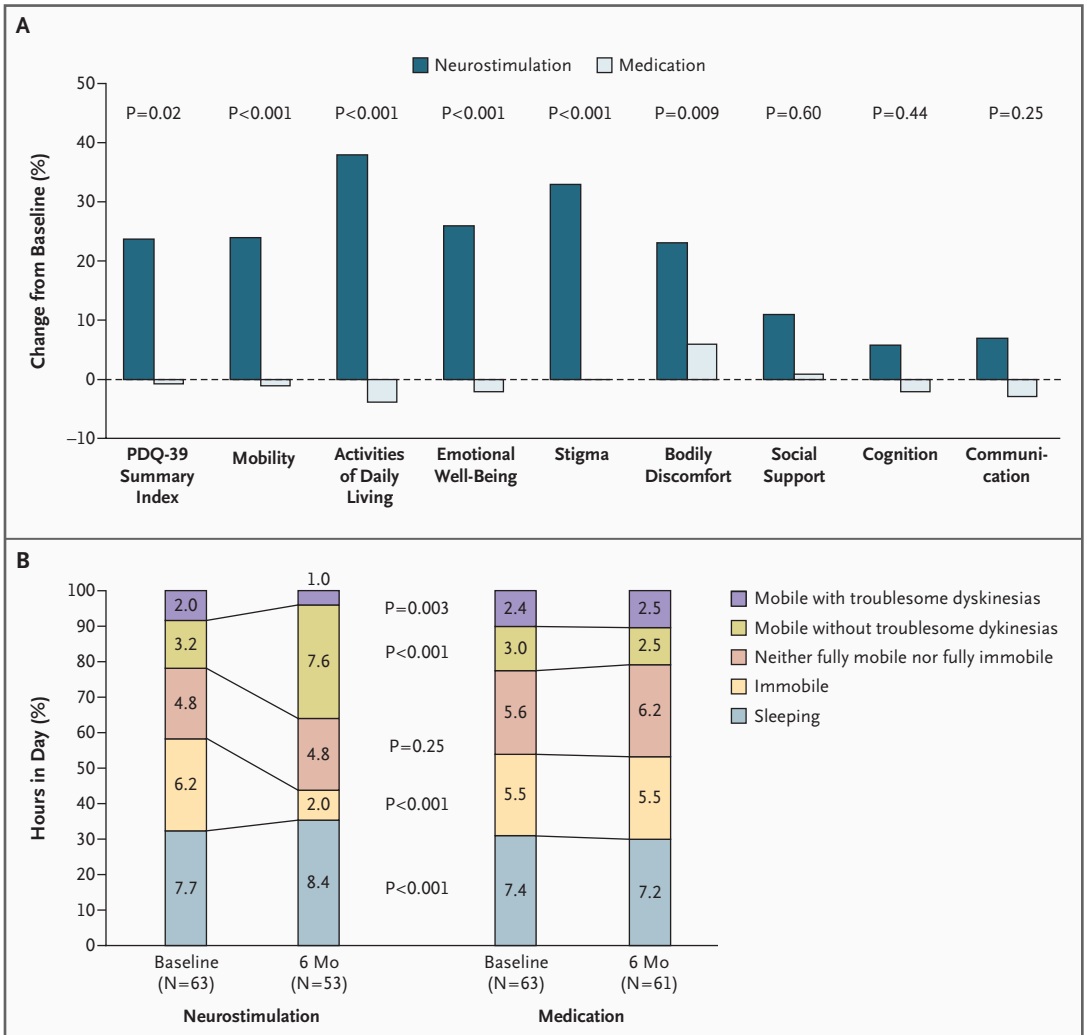

Figure 2. Changes in PDQ-39 Subscores (Panel A) and Patients' Diaries (Panel B) from Baseline to Six Months in the Neurostimulation and Medication Groups.

Panel A shows changes in the PDQ-39 subscores (percentage of baseline values) for the two groups. The subscores evaluate various domains of quality of life. Significant changes occurred only in the neurostimulation group. The greatest improvements occurred in activities of daily living, stigma of the disease, and emotional well-being. The subscores for mobility and bodily discomfort were improved to the same extent as the summary index. There was no significant improvement in social support, cognition, or communication. Panel B shows the results of the diaries kept by the patients. For each 30-minute interval throughout the day, the patients recorded whether they were mobile with troublesome dyskinesias, mobile without troublesome dyskinesias, neither fully mobile nor fully immobile, immobile, or asleep. The graph shows the percentage of hours in a day spent in each condition at baseline and six months for the two treatment groups. Significant changes occurred only in the group receiving neurostimulation, with longer periods of mobility, shorter periods of immobility, shorter periods with troublesome dyskinesias, and longer periods of sleep. The numbers on the bars indicate the mean number of hours spent in each category. P values are for the differences in improvement between the neurostimulation group and the medication-only group.

lation and the medication groups, but the mental summary score of the SF-36 showed a small but significant improvement of 7 percent in the neurostimulation group (Table 3).

Scores on the dyskinesia scale obtained while the patient was not taking medication improved from 6.7±5.3 to 3.1±3.5 (54 percent) in the neurostimulation group but remained unchanged in the medication group. The patients' diaries showed profound and significant changes from baseline to six months in the neurostimulation group alone (Fig. 2B). The period of immobility was reduced

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by 4.2 hours and the period of mobility without dyskinesias was increased by 4.4 hours. The time spent sleeping was increased by 0.7 hour. The period of mobility with troublesome dyskinesias was also significantly reduced.

The mean values for the stimulation settings were as follows: amplitude, 2.9±0.6 V; frequency, 139±18 Hz; and pulse duration, 63±7.7 μsec. The dopaminergic equivalents were reduced by 50 percent for the neurostimulation group and by 8 percent for the medication group (Table 3).

ADVERSE EVENTS

Thirteen severe adverse events were reported in 13 patients: 10 in the neurostimulation group and 3 in the medication group (12.8 percent and 3.8 percent, respectively; P=0.04) (Table 4). Three patients died in the neurostimulation group: one died as a result of intracerebral hematoma incurred during surgery, one died from pneumonia that developed six weeks after randomization, and one committed suicide five months after randomization. One patient in the medication group died in a motor vehicle accident, caused because he was driving during a psychotic episode. All other severe adverse events resolved without permanent complications (Table 4). A total of 173 adverse events were reported in 89 patients: 39 (50.0 percent) in the neurostimulation group and 50 (64.1 percent) in the medication group (P=0.08). Most adverse events were well-known medical problems associated with advanced Parkinson's disease.

DISCUSSION

This trial demonstrated the superior efficacy of neurostimulation over best medical management in patients with advanced Parkinson's disease and levodopa-related motor complications. Previous "proof-of-principle" studies,[5,6] which did not include prospective control groups, showed that subthalamic neurostimulation improved fluctuating mobility and dyskinesias for up to five years.[7] In our study, neurostimulation was associated with a 25 percent improvement in the PDQ-39 summary index, which is within the range of the improvements described in uncontrolled case series[21,22] and is consistent with the 22 percent improvement in the SF-36, a generic quality-of-life scale.

In contrast to many previous studies of Parkinson's disease, which focused on motor scales, we used quality-of-life measures as the primary outcome criteria.[5,7,23-25] Factors in addition to motor function contribute to such a complex variable as the quality of life. First, complications of surgery or medication are frequent and may decrease the quality of life, despite improvement in motor signs. Second, there is an ongoing discussion about whether the detrimental effects on cognition,[26,27] mood,[28] and behavior[29] that have been observed in prior studies of neurostimulation were related to surgery, to stimulation itself, or to disease, medication, or a potential selection bias. Finally, depression has a greater effect than motor symptoms on the quality of life,[30] so that neuropsychiatric adverse effects could cancel out motor benefits. Therefore, a controlled clinical trial measuring the quality of life was necessary. Our findings suggest that despite all these possible confounders, neurostimulation is superior to medical treatment alone for patients similar to those in our study.

How strong are the clinical effects of neurostimulation? Before surgery, the PDQ-39 summary index scores of the patients in the study were similar to those of a group of patients who needed help in everyday situations,[31] and after surgery, their scores were similar to those of a mobile cohort without balance problems.[31] The effects of neurostimulation can also be compared with the effects of drugs, which are usually smaller. For example, a placebo-controlled trial of rasagiline showed a significant improvement of 2.9 points[32] in the PDQ-39 summary index, and a trial of entacapone, a drug with a well-documented effect on the motor score,[33] showed no improvement in the quality of life.[34] Finally, the minimum clinically relevant difference (i.e., the difference that a patient would consider to be an improvement) in the score for the PDQ-39 summary index can be used as an estimate of the strength of treatment effects.[35] In one study, this difference was found to be 0.6 point.[35] Thus, the improvement of about 10 points observed in our study would be considered to represent a strong effect.

What accounts for this strong improvement? Improvements in the scores on the PDQ-39 subscales for mobility and activities of daily living reflect changes in motor aspects of the disease. Indeed, evaluation of motor performance by means of the UPDRS-III, the dyskinesia scale, and patients' diaries mainly documented a decrease in the severity and duration of periods of immobility and a decrease in the duration and severity of periods of dyskinesias among patients who received neurostimulation. Scores for emotional

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Table 4. Adverse Events during the Six-Month Study.*

Event	Neurostimulation Group	Medication Group
	no. of events	
Serious adverse event†		
Death	3	1
Perioperative cerebral hematoma	1	0
Suicide 5 mo after surgery	1	0
Car accident during psychotic episode	0	1
Pneumonia	1	0
Readmission to the hospital	7	2
Worsening of mobility	3	1
Infection at the stimulator site	2	0
Erroneous stimulator shut-off	1	0
Vertebral fracture from fall	1	0
Hip fracture from fall	0	1
Total nonserious adverse events‡	77	96
Mild	35	8
Moderate	32	39
Severe	10	49
Nonserious adverse event related to surgery§		
Subcutaneous seroma (moderate)	4	0
Asymptomatic intracerebral hematoma (mild)	2	0
Postoperative confusion		
Mild	1	0
Moderate	3	0
Skin erosion (mild)	3	0
Extension cable discomfort (moderate)	2	0
Pneumonia (severe)	1	0
Other adverse event (mild)	1	0

well-being, stigma, and bodily discomfort also improved, resulting in an improvement in the overall quality of life in the neurostimulation group. We did not find significant changes in the neuropsychologic and psychiatric evaluations. Changes in cognition or mood that may occur in individual patients as side effects of surgery or stimulation[26-28] therefore did not seem to decrease the quality of life in the neurostimulation group as a whole.

Neurostimulation resulted in major benefits in our study, but some limitations of the study design need to be critically addressed. There was no sham-surgery group or placebo control. The use of sham surgery as a control remains controversial because of the potential side effects.[36] A feasible option would be to administer placebo stimulation for a short period in a patient who is not taking medication in order to compare motor signs in the stimulated and the nonstimulated condition.[5] Stimulation of the subthalamic nucleus interferes with antiparkinsonian medication, and a large decrease in the dose of such medications is mandatory to prevent motor and behavioral side effects. Therefore, a blinded comparison of neurostimulation with best medical treatment was not feasible. The control group was treated by experts in movement disorders in compliance with national guidelines for the treatment of advanced Parkinson's disease,[9] but further standardization of the best medical treatment was not performed.

In conclusion, this six-month study demonstrated that subthalamic neurostimulation resulted

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Table 4. (Continued.)

Event	Neurostimulation Group	Medication Group
	no. of events	
Nonserious adverse event related to stimulation or medication¶		
Severe fluctuations in mobility requiring outpatient visits		
Mild	4	1
Moderate	1	13
Severe	2	30
Dyskinesia requiring outpatient visits		
Mild	7	3
Moderate	9	19
Severe	4	19
Dysarthria		
Mild	5	0
Moderate	3	0
Depression (moderate)	4	0
Cognitive disturbances		
Mild	2	0
Moderate	1	0
Psychosis		
Mild	0	4
Moderate	3	3
Severe	1	0
Loss of affect (severe)	1	0
Other adverse events		
Mild	10	0
Moderate	2	4
Severe	1	0

* Adverse events related either to surgery or to stimulation or medication were classified as mild, moderate, or severe. The omission of a level of severity indicates that no patients had that degree of severity.
† A total of 13 patients had a severe adverse event, and 89 had an adverse event.
‡ Total includes all adverse events related either to surgery or to stimulation or medication.
§ This category included 17 adverse events.
¶ This category included 156 adverse events.

in a significant and clinically meaningful improvement in the quality of life of patients under 75 years of age who had advanced Parkinson's disease with severe fluctuations in mobility and dyskinesia. The patients who received neurostimulation had longer periods and better quality of mobility with less dyskinesia. These changes in motor functioning led to improvement in measurements of activities of daily living, emotional well-being, stigma, and bodily discomfort. Cognition, mood, and overall psychiatric functioning were unchanged. In carefully selected patients, neurostimulation of the subthalamic nucleus is a powerful treatment that alleviates the burden of advanced Parkinson's disease. The prospect of an improved quality of life in patients treated with neurostimulation has to be weighed against the risk of complications related to surgery.

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REFERENCES

1. 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.
2. Martinez-Martin P. An introduction to the concept of "quality of life in Parkinson's disease." J Neurol 1998;245:Suppl 1:S2-S6.
3. Goetz CG, Poewe W, Rascol O, Sampaio C. Evidence-based medical review update: pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004. Mov Disord 2005;20:523-39.
4. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. N Engl J Med 2000;342:1484-91.
5. The Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 2001; 345:956-63.
6. Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 1998;339:1105-11.
7. 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.
8. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181-4.
9. Oertel W, Deuschl G, Eggert K, et al. Parkinson-Syndrome. In: Diener HC, ed. Leitlinien für Diagnostik und Therapie in der Neurologie: Stuttgart: Thieme-Verlag, 2003:38-57.
10. Berger K, Broll S, Winkelmann J, et al. Untersuchung zur Reliabilität der deutschen Version des PDQ-39: Ein krankheitsspezifischer Fragebogen zur Erfassung der Lebensqualität von Parkinson-Patienten. Akt Neurol 1999;26:180-4.
11. Peto V, Jenkinson C, Fitzpatrick R, Greenhall R. The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. Qual Life Res 1995;4:241-8.
12. Fahn S, Elton RL. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne D, Goldstein M, eds. Recent developments in Parkinson's disease. Florham Park, N.J: MacMillan Health Care Information, 1987:153-63.
13. Marconi R, Lefebvre-Caparros D, Bonnet AM, Vidailhet M, Dubois B, Agid Y. Levodopa-induced dyskinesias in Parkinson's disease: phenomenology and pathophysiology. Mov Disord 1994;9:2-12.
14. Matthis S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellak L, Karatsu TB, eds. Geriatric psychiatry: a handbook for psychiatrists and primary care physicians. New York: Grune & Stratton, 1976:77-121.
15. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-9.
16. Flemenbaum A, Zimmermann RL. Inter- and intra-rater reliability of the Brief Psychiatric Rating Scale. Psychol Rep 1973; 32:783-92.
17. Bullinger M, Kirchberger I. SF-36, Fragebogen zum Gesundheitszustand: Handanweisung. Göttingen, Germany: Hogrefe, 1998.
18. Martinez-Martin P, Valldeoriola F, Molinuevo JL, Nobbe FA, Rumia J, Tolosa E. Pallidotomy and quality of life in patients with Parkinson's disease: an early study. Mov Disord 2000;15:65-70.
19. Fleming TR, Harrington DP, O'Brien PC. Designs for group sequential tests. Control Clin Trials 1984;5:348-61.
20. Hoehn MM, Yahr MD. Parksonism: onset, progression and mortality. Neurology 1967;17:427-42.
21. Martinez-Martin P, Valldeoriola F, Tolosa E, et al. Bilateral subthalamic nucleus stimulation and quality of life in advanced Parkinson's disease. Mov Disord 2002; 17:372-7.
22. Lezcano E, Gomez-Esteban JC, Zarranz JJ, et al. Improvement in quality of life in patients with advanced Parkinson's disease following bilateral deep-brain stimulation in subthalamic nucleus. Eur J Neurol 2004;11:451-4.
23. 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.
24. Schupbach WM, Chastan N, Welter ML, et al. Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up. J Neurol Neurosurg Psychiatry 2005;76:1640-4.
25. 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.
26. Saint-Cyr JA, Trepanier LL, Kumar R, Lozano AM, Lang AE. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. Brain 2000;123: 2091-108.
27. Ardouin C, Pillon B, Peiffer E, et al. Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. Ann Neurol 1999;46:217-23.
28. Berney A, Vingerhoets F, Perrin A, et al. Effect on mood of subthalamic DBS for Parkinson's disease: a consecutive series of 24 patients. Neurology 2002;59:1427-9.
29. Houeto JL, Mesnage V, Mallet L, et al. Behavioural disorders, Parkinson's disease and subthalamic stimulation. J Neurol Neurosurg Psychiatry 2002;72:701-7.
30. Global Parkinson's Disease Survey Steering Committee. Factors impacting on quality of life in Parkinson's disease: results from an international survey. Mov Disord 2002;17:60-7.
31. Schrag A, Jahanshahi M, Quinn N. How does Parkinson's disease affect quality of life? A comparison with quality of life in the general population. Mov Disord 2000;15:1112-8.
32. Biglan KM, Schwid S, Eberly S, et al. Rasagiline improves quality of life in patients with early Parkinson's disease. Mov Disord 2006;21:616-23.
33. Poewe WH, Deuschl G, Gordin A, Kultalahti ER, Leinonen M. Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: a 6-month randomized placebo-controlled double-blind study in Germany and Austria (Celomen study). Acta Neurol Scand 2002;105:245-55.
34. Reichmann H, Boas J, Macmahon D, Myllyla V, Hakala A, Reinikainen K. Efficacy of combining levodopa with entacapone on quality of life and activities of daily living in patients experiencing wearing-off type fluctuations. Acta Neurol Scand 2005;111:21-8.
35. Peto V, Jenkinson C, Fitzpatrick R. Determining minimally important differences for the PDQ-39 Parkinson's disease questionnaire. Age Ageing 2001;30:299-302.
36. Kim SY, Frank S, Holloway R, Zimmerman C, Wilson R, Kieburtz K. Science and ethics of sham surgery: a survey of Parkinson disease clinical researchers. Arch Neurol 2005;62:1357-60.

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