

Bilateral Deep Brain Stimulation of the Globus Pallidus to Treat Tardive Dyskinesia

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Context: Tardive dyskinesia (TD) is a common and potentially disabling disorder induced by use of antipsychotic drugs for which medical treatment often gives disappointing results.

Objective: To assess the efficacy of bilateral deep brain stimulation of the internal part of the globus pallidus to treat severe TD.

Design: Prospective phase 2 multicenter study.

Setting: Six French university hospitals.

Patients: Patients with severe TD refractory to medical treatment were studied to evaluate the severity of abnormal involuntary movements before and after 6 months of bilateral globus pallidus deep brain stimulation. A 2-step open Fleming procedure was used to avoid unnecessary accrual of patients. A successful outcome was defined as a decrease of more than 40% in the main outcome measure at 6 months. The early stopping rule was invoked if the number of successful outcomes in 10 patients was fewer than 2, or 5 or more. A double-blind evaluation in the presence and absence of stimulation was performed at 6 months after surgery.

Main Outcome Measure: Change in score on the Extrapyramidal Symptoms Rating Scale.

Results: At 6 months after surgery, the Extrapyramidal Symptoms Rating Scale score had decreased compared with baseline by more than 40% (mean improvement, 61%; range, 44%-75%) in the first 10 patients included. In accord with the 2-step open Fleming procedure, we ended the trial at the first step and concluded that pallidal stimulation is an effective treatment for TD. The efficacy of the treatment was confirmed by a double-blind evaluation, with a mean decrease of 50% (range, 30%-66%) ($P=.002$) in the Extrapyramidal Symptoms Rating Scale score when stimulation was applied compared with the absence of stimulation. There were no marked changes in the patients' psychiatric status.

Conclusion: Although these results need to be confirmed in a larger group of patients with a longer follow-up, bilateral globus pallidus deep brain stimulation seems to offer a much-needed new treatment option for disabling TD.

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TARDIVE DYSKINESIA (TD) IS a common and potentially disabling adverse effect of antipsychotic treatment.¹ The spectrum of symptoms is wide and includes (1) involuntary, often rapid, repetitive abnormal movements (choreic movements), typically affecting the mouth and the tongue but sometimes localized to the limbs or trunk, and (2) sustained muscle contraction leading to abnormal axial posture (ie, dystonia), which often dominates the clinical picture in young subjects.² With conventional use of antipsychotics, the incidence of TD is about 5% per year of treatment in adults³ and rises to 25% to 30% in older persons.⁴ Although occurring less frequently, TD has been re-

ported with the use of new-generation antipsychotics.⁵ In about 10% of patients, TD is considered to be moderate or severe⁶ and can be troublesome because of disfigurement or functional impairment (eg, breathing, eating, and walking). Treatment is problematic. A first option is the withdrawal of antipsychotic regimen, which is controversial. Although some patients show noticeable improvement following withdrawal of treatment with antipsychotics, complete and lasting resolution of TD is rare, and the cessation of antipsychotic use in psychotic patients increases the risk of a relapse.⁷ Therefore, such an option can only be considered in patients for whom antipsychotic treatment is not considered necessary. In the remaining patients, the preferred option when they are

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Group Members: A list of the other members of the French Stimulation for Tardive Dyskinesia (STARDYS) Study Group appears at the end of this article.

Table 1. Characteristics of Patients at Inclusion

Patient No./ Sex/Age, y*	Reason for Treatment With Antipsychotics	Duration of TD, y†	Duration of Antipsychotic Treatment Before TD‡	Dystonia				Choreic Movements				MADRS§	PANSS			Psychiatric Treatment**	TD Suppressive Treatment
				UL	LL	F	Ax	UL	LL	F	Ax		+	-¶	GP#		
1/F/40	Depression	2	3 mo	0	0	0	+	0	0	0	0	44	9	22	61	Mianserin a benzodiazepine	Trihexyphenidyl
2/F/33	Depression	6	5.5 y	+	+	0	0	+	0	+	0	3	19	13	26	0	Trihexyphenidyl, tetrabenazine
3/F/69	Depression	9	5 y	0	0	+	+	0	0	+	+	8	9	11	24	Olanzapine, mianserin	Trihexyphenidyl
4/M/45	Depression	3	6 y	+	0	+	+	+	0	+	0	16	11	12	38	Venlafaxine, a benzodiazepine	0
5/M/51	Schizophrenia	3	5 y	+	+	+	+	+	+	+	+	14	7	12	28	Clozapine, a benzodiazepine	0
6/F/43	Schizophrenia	4	20 y	0	0	0	+	+	0	0	0	5	12	10	24	Olanzapine, a benzodiazepine	Trihexyphenidyl
7/F/56	Depression	3	4 mo	+	+	0	0	0	0	0	0	6	8	7	20	Citalopram hydrobromide, a benzodiazepine	0
8/F/27	Schizophrenia	1	5 y	+	0	0	+	0	0	0	0	7	10	10	23	Amisulpride, a benzodiazepine	Trihexyphenidyl
9/M/26	Childhood disintegrative disorder	4	2 y	0	0	0	+	+	0	0	0	4	15	21	33	Valpromide, olanzapine, a benzodiazepine	Baclofen
10/F/61	Depression	10	1 y	+	+	0	+	0	0	+	0	8	8	7	21	Clomipramine, amitriptyline hydrochloride, a benzodiazepine	Trihexyphenidyl

Abbreviations: Ax, axial; F, face; LL, lower limb; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale (with +, positive score; -, negative score; and GP, general psychopathology score); TD, tardive dyskinesia; UL, upper limb.

*Mean ± SEM age, 45.0 ± 4.5 years.

†Mean ± SEM duration, 4.5 ± 1.0 years.

‡Mean ± SEM duration, 5 ± 2 years.

§Mean ± SEM score, 11.5 ± 4.0.

||Mean ± SEM score, 11 ± 1.

¶Mean ± SEM score, 12.5 ± 1.5.

#Mean ± SEM score, 30 ± 4.

**Benzodiazepine and clozapine were used for treating anxiety and TD; olanzapine was used solely for treating TD.

being treated with conventional antipsychotics is to replace these with new-generation antipsychotics. Despite the lack of any clear demonstration of efficacy, this approach has had some success and is accepted and recommended.⁸ When these 2 strategies fail and TD is still bothersome, suppressive treatment is considered. In addition to their low risk of TD, new-generation antipsychotics, especially clozapine, have shown some efficacy in reducing or stopping abnormal movements in patients for whom antipsychotics had been withdrawn.⁸ Many other drugs (eg, vitamin E, tetrabenazine, benzodiazepines, calcium channel blockers, and noradrenergic antagonists) have shown some efficacy.^{7,8} To our knowledge, the efficacy of none of these suppressive treatments has been demonstrated by controlled clinical investigations.⁷ In some patients, distressing TD may persist and lead to disability.

During the past 20 years, there has been a renewed interest in surgical treatment in the field of movement disorders. Pallidotomy and bilateral continuous deep brain stimulation (DBS) applied to the internal part of the globus pallidus (GPi) have been shown to be effective treatments to improve various abnormal involuntary movements, such as levodopa-induced dyskinesia in Parkinson

disease,⁹ primary¹⁰ or secondary¹¹ dystonia, and chorea in Huntington disease.¹² Although its pathophysiology is not well understood, TD may have some mechanisms in common with these abnormal movement disorders, such as a dysfunction of the GPi.¹³ Indeed, beneficial effects of pallidotomy^{14,15} and DBS applied to the GPi¹⁶⁻¹⁹ have been reported in a few cases of TD. To assess the efficacy of pallidal stimulation in treating TD, we conducted a prospective phase 2 multicenter study using a double-blind evaluation in the presence and absence of stimulation at 6 months after surgery.

METHODS

PATIENTS

Ten patients (**Table 1**) experiencing severe TD were included in this pilot study. All patients had taken conventional antipsychotics for longer than 3 months to treat major depressive disorder (6 patients), schizophrenia (3 patients), or childhood disintegrative disorder (1 patient) (diagnosis by the referring psychiatrist for the study in each center was based on DSM-IV criteria). The patients had developed TD from a few weeks to several years after the initiation of treatment. Despite

withdrawal of treatment with neuroleptics or their replacement with new-generation antipsychotics, severe TD had persisted for more than 12 months. All of the patients had functional disability (ie, pain, gait disturbances, or hand disability); 9 patients also found their abnormal involuntary movements socially embarrassing, with patient 1 being partially anosognosic of the disorder. Various TD suppressive treatments had been tried in these patients but were insufficiently effective to improve their motor disability. As an inclusion criterion for the study, a previous attempt at treatment using clozapine or tetrabenazine at the maximum tolerated dosage for at least 4 weeks was required. Tardive dyskinesia suppressive treatments were maintained at the beginning of the study if they were tolerated and if they led to some improvement. Before inclusion, the history and clinical characteristics of each patient were reviewed at investigators' meetings (comprising investigators from 6 centers in the study and at least 2 neurologists, 2 psychiatrists, and 2 neurosurgeons) to confirm that all inclusion criteria were fulfilled (eg, diagnosis, psychiatric status, level of disability, and attempts at treatment of TD). The 10 patients in the study were consecutively included from among 18 cases reviewed at 3 meetings during a 2-year period. At the time of surgery, 5 patients (patients 2, 3, 4, 7, and 10) were free of psychiatric disorders; patient 1 had persistent depression stabilized by antidepressant use, and chronic psychosis in patients 5, 6, 8, and 9 was satisfactorily controlled by antipsychotic treatment (ie, absence of active delusions or delirium and low scores on the Positive and Negative Syndrome Scale). None of them had a profound deficit of cognitive function (all patients had a Mini-Mental State Examination²⁰ score of ≥ 24 , except for patient 8 with a score of 22); 5 patients had alteration of executive function, with Mattis Dementia Scale scores²¹ of less than 130 (lowest score, 116). Findings from neurological examinations were unremarkable except for abnormal movements and mild to moderate cognitive alteration in 5 patients, and brain magnetic resonance imaging was normal except for mild atrophy. The study protocol was approved by the Ethics Committee of Centre Hospitalier Universitaire de Nantes, and all patients gave their written informed consent.

SURGERY AND SETTING OF STIMULATION PARAMETERS

Stimulation leads were implanted bilaterally in the posteroventral part of the GPi by stereotaxic surgery under local anesthesia (3 patients) or general anesthesia (7 patients with severe neck dystonia rendering surgery under local anesthesia impossible). Targeting of the GPi was based on preoperative magnetic resonance imaging (coupled with ventriculography in 5 patients) and intraoperative stimulation test results (ie, looking for a stimulation-induced visual flash [indicating the proximity of the optical tract, which is close to the posteroventral part of the GPi] and for stimulation-induced dystonia [indicating current spreading to the internal capsule and too internal a position of the lead when observed for a voltage < 3 V]). Patients under general anesthesia were briefly awake for the intraoperative assessment of the effects of stimulation. One to 5 exploratory tracks were performed to determine the best trajectory for implanting the definitive lead. Postoperative magnetic resonance imaging was used to verify the correct placement of the leads and to calculate electrode coordinates.²² The leads were then connected to a pulse generator (Kinetra; Medtronic, Minneapolis, Minn) implanted in the subclavicular region.

One month after surgery, stimulation parameters were set during a 3- to 5-day session. The effects of stimulation applied through each electrode of each lead were assessed using in-

creasing voltage²³ to detect stimulation-induced adverse effects, such as dystonia and dysarthria. Stimulation was unipolar, and the frequency and pulse width of the stimulation current were kept at 130 Hz and 150 microseconds, respectively. The lowest electrode that did not induce such adverse effects at voltages less than 3 V was chosen for application of 2.5-V chronic stimulation. If no improvement was observed after 24 hours, the voltage was increased up to the maximum tolerated voltage, without exceeding 5 V. The patient was assessed after at least 1 week of stimulation at that voltage. In the event of an absence of improvement, the same procedure was applied to the upper adjacent electrode.

CLINICAL EVALUATION

The severity of TD was assessed before (baseline) and at 3 and 6 months after surgery using the following: the Extrapyrimal Symptoms Rating Scale (ESRS) score,²⁴ the Abnormal Involuntary Movement Scale score,²⁵ and a 4-point patient Clinical Global Impression score (0, worsening or no improvement; 1, mild; 2, moderate; and 3, major improvement [with the score given by the caregiver for patient 8]). The 3- and 6-month assessments were performed following at least 4 weeks of unchanged stimulation parameters. At 6 months, we performed a double-blind evaluation of the effects of stimulation. The 2 stimulation conditions (stimulation on and stimulation off) were applied on 2 consecutive days (at the same time of day for any given patient) in a counterbalanced order across patients. The stimulator was turned on or off by a study nurse in accord with written instructions as to the order of stimulation conditions to apply, which was supplied by the study coordinator. Neither the patient nor the rating investigator was aware of which condition was being applied, and the patient was instructed not to talk to the rating investigator during the evaluation. The period between the application of the stimulation condition and the assessment of the ESRS score differed among patients (range, 2-12 hours) and corresponded to the withdrawal period of stimulation determined at month 3 that produced a reappearance of the symptoms. Patients were scored on the Montgomery-Asberg Depression Rating Scale, Positive and Negative Syndrome Scale, Mini-Mental State Examination, Mattis Dementia Scale, Frontal Assessment Battery,²⁶ and Frontal Behavior Scale²⁷ before surgery and at 6 months after surgery. Careful psychiatric monitoring of patients was performed with a systematic psychiatric consultation before and at 1, 3, and 6 months after surgery; intermediate visits were scheduled, if required. In the event of an improvement in motor symptoms, TD suppressive pharmacological treatment could be reduced or withdrawn during the study.

STATISTICAL ANALYSIS

A 2-step open Fleming procedure²⁸ was used to assess the efficacy of pallidal stimulation on TD. This procedure provides for early stopping to avoid continuing the accrual of patients if the success response rate is not acceptable or is sufficiently of interest. A successful outcome was defined as a decrease of more than 40% in the main outcome measure (the ESRS score) at 6 months. The design was based on the null hypothesis H_0 that a success response rate of 15% or less would be of no clinical interest. If the success response rate was at least 50% (alternative hypothesis H_1), pallidal stimulation would be considered to be of definite clinical interest. Based on these hypotheses, it was necessary to include 21 patients considering $\alpha = .05$ and $\beta = .10$ in a single-step procedure in which 10 patients were planned to be included. If 0 or 1 success was observed, the study would be stopped (acceptance of H_0). If 5 or

more successes were observed, the study would be stopped (rejection of H_0). If 2, 3, or 4 successes were observed, 11 additional patients would then be included for the remainder of the study. The probability of early stopping at the first step was 55.4%, and the probability of continuing was 44.6%.

Mixed models and Wilcoxon paired tests were used to evaluate changes in the different scores before and after pallidal stimulation and to compare the ESRS scores in the double-blind evaluation. Statistical analyses were performed using Splus version 6.2 software (Insightful Corporation, Seattle, Wash).

RESULTS

All patients showed progressive improvement in the days or weeks following the initiation of pallidal stimulation. The improvement in choreic movements usually occurred within several days, whereas the total improvement in axial posture dystonia took several weeks. At 6 months after surgery, the ESRS scores had decreased compared with baseline by more than 40% among the first 10 patients included. In accord with the 2-step open Fleming procedure, the trial was stopped, and we concluded that pallidal stimulation is an effective treatment for TD ($\alpha = .032$ and $\beta = .043$). The mean ESRS score ($P < .001$) and the mean Abnormal Involuntary Movement Scale score ($P < .001$) decreased significantly after surgery. At 3 months after surgery, the decrease compared with baseline was 61% (range, 19%-86%) for the ESRS score ($P = .002$) and 56% (range, 32%-81%) for the Abnormal Involuntary Movement Scale score ($P = .006$). The improvement was maintained at 6 months, with decreases compared with a baseline of 61% (range, 44%-75%) for the ESRS score ($P = .005$) and of 56% (range, 33%-69%) for the Abnormal Involuntary Movement Scale score ($P = .006$) (**Figure 1**). All 10 patients (with caregiver assessment being provided for the patient who was partially anosognosic) considered that there was major improvement in their abnormal involuntary movements. Two patients were free of dyskinesia, and the others had mild abnormal movements that they considered not to be troublesome. Tardive dyskinesia suppressive treatment was reduced in 5 patients (**Table 2**). There was similar improvement in the dystonic and choreic components of TD. Compared with baseline, the ESRS dystonia score (component III) was decreased by 67% (range, 17%-93%) at month 3 ($P = .002$) and by 68% (range, 28%-89%) at month 6 ($P = .006$), and the ESRS choreic movements score (component IV) was decreased by 62% (range, 33%-91%) at month 3 ($P = .006$) and by 53% (range, 27%-75%) at month 6 ($P = .006$) (**Figure 2**). Six patients had mild parkinsonian symptoms and akathisia (component II of the ESRS) that had improved by 27% to 100% at 6 months after surgery. All active electrodes were located within the posterolateral part of the GPi (mean \pm SEM coordinates, 20.1 \pm 0.4 mm lateral to the median line, 15.3 \pm 0.5 mm anterior to the posterior commissure, and 3.9 \pm 0.4 mm below the bicommissural line). Continuous monopolar stimulation was applied in all of the patients (mean \pm SEM voltage, 3.5 \pm 0.2 V; pulse width, 150 microseconds; and frequency, 130 Hz at 6 months). At 6 months, the double-blind evaluation confirmed the

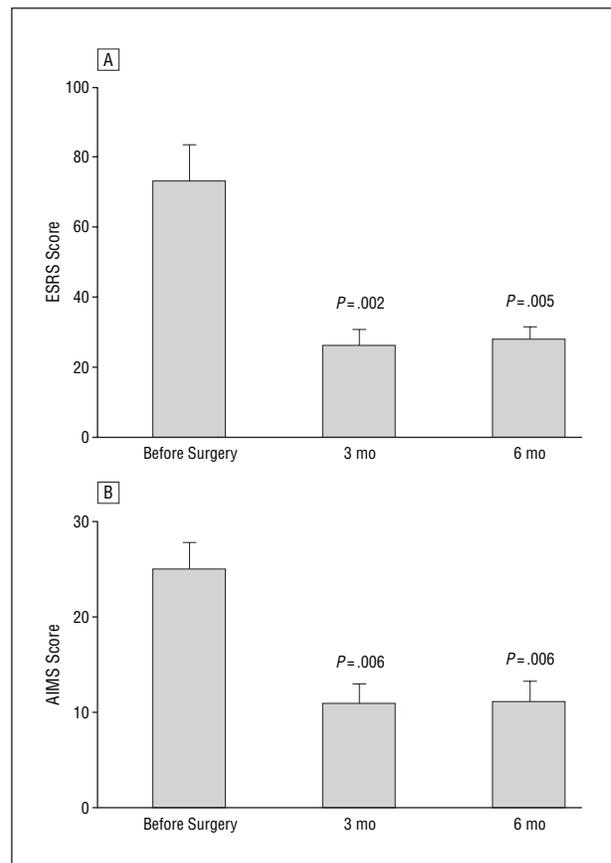


Figure 1. Effects of continuous pallidal stimulation on tardive dyskinesia at 3 and 6 months after surgery. Before surgery and at 3 and 6 months after surgery, the mean \pm SEM scores for motor symptoms were assessed using the Extraparal Symptoms Rating Scale (ESRS) (maximum score, 236) (A) and the Abnormal Involuntary Movement Scale (AIMS) (maximum score, 40) (B). Limit lines indicate SEM.

efficacy of bilateral stimulation, with a mean decrease of 50% (range, 30%-66%) ($P = .002$) in the ESRS score when stimulation was applied compared with the off stimulation condition. Depressed mood improved in patient 1 (Montgomery-Asberg Depression Rating Scale score, 44 at baseline to 10 at 6 months after surgery) and worsened in 3 patients (from 3 to 26 in patient 2, from 14 to 23 in patient 5, and from 6 to 21 in patient 7) who did not meet *DSM-IV* criteria for major depressive disorder and did not require specific treatment except for the use of antidepressant therapy in 1 patient. None of the patients developed delusions or delirium during the post-operative period (mean \pm SEM Positive and Negative Syndrome Scale score, 11 \pm 1 before surgery and 10 \pm 1 at 6 months after surgery). There were no marked changes in antipsychotic or antidepressant treatment. No changes were observed in the patients' cognitive status (mean \pm SEM Mini-Mental State Examination score, 26.7 \pm 0.9 before surgery vs 26.8 \pm 0.4 at 6 months after surgery; Mattis Dementia Scale score, 130.5 \pm 2.5 vs 134.8 \pm 2.0; Frontal Assessment Battery score, 15.7 \pm 0.6 vs 16.3 \pm 0.3; and Frontal Behavior Scale score, 2.3 \pm 0.6 vs 2.4 \pm 0.7). Two serious adverse events occurred. Patient 5, with no beneficial effects of stimulation and in whom the position of the left lead was too lateral and an-

Table 2. Effects of Continuous Pallidal Stimulation at 6 Months After Surgery

Patient No.	Before Surgery		6 Months After Surgery		Stimulating Electrode, R (x, y, z)/L (x, y, z)	Voltage, R/L, V	Changes in TD Suppressive Treatment
	ESRS*	AIMS†	ESRS‡	AIMS§			
1	39	12	22	6	1 (18, 12.5, 5)/0 (18, 12.5, 4.5)	3.5/3.7	0
2	78	26	21	10	1 (22.5, 19, 3)/1 (22, 19, 4)	3.2/3.6	↓Trihexyphenidyl ↓Tetrabenazine
3	80	34	45	22	1 (20, 16, 3)/1 (23, 18, 2.5)	3.6/3.6	↓Olanzapine ↓Trihexyphenidyl
4	99	31	25	13	0 (20, 14, 6)/1 (21, 14, 5)	3/3.4	0
5	133	35	57	22	0 (19.5, 14, 7.5)/1 (20, 14, 6.5)	3.8/3.8	↓Clozapine ↓Benzodiazepine
6	35	15	9	5	0 (16.5, 16.5, 3.5)/0 (21, 15.5, 4)	5/5	0
7	74	18	28	12	1 (21, 16.5, 2.5)/1 (16, 17.5, 3)	3.5/3.5	↓Benzodiazepine
8	90	27	29	6	1 (22, 16.5, 0)/1 (22, 13, 0)	2.5/3.2	0
9	31	16	16	5	1 (20, 12, 6)/0 (20, 12, 5)	2.6/2.8	0
10	72	36	26	12	1 (20, 16.5, 4)/1 (20, 16.5, 4)	3.5/3.6	↓Trihexyphenidyl ↓Benzodiazepine

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; ESRS, Extrapyrimal Symptoms Rating Scale; L, left; R, right; TD, tardive dyskinesia; ↓, decreased dosage of medication; †, discontinued use of medication.

*Mean ± SEM score, 73.1 ± 10.0.

†Mean ± SEM score, 25 ± 3.

‡Mean ± SEM score, 28.0 ± 4.5; *P* = .005.

§Mean ± SEM score, 11 ± 2; *P* < .006.

||Stimulating electrodes are numbered from 0 to 3, with 0 being the lowest and 3 being the highest, with 1.5 mm between 2 adjacent electrodes (Talraich coordinates: x, lateral to the median line; y, anterior to the posterior commissure, and z, below the bicommissural line).

|||The Talraich coordinates x, y, and z of the left lead (electrode 0) before reimplantation were 21.5, 16, and 4, respectively.

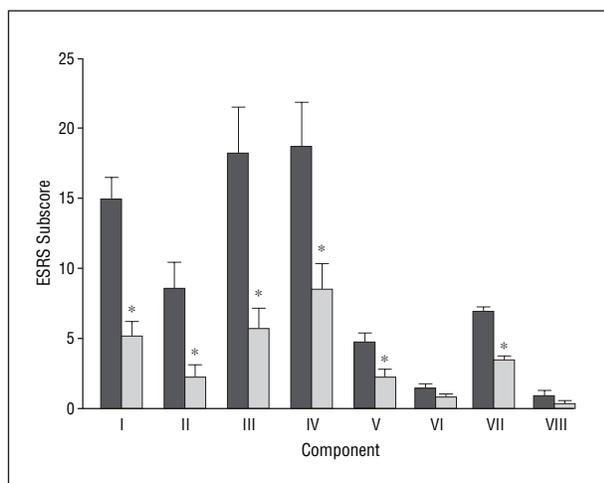


Figure 2. Effects of continuous pallidal stimulation on the subscores of the Extrapyrimal Symptoms Rating Scale (ESRS) at 6 months after surgery. Before surgery (black bars) and at 6 months after surgery (gray bars), the mean ± SEM scores were assessed using the questionnaires on extrapyramidal symptoms (component I; maximum score, 36), parkinsonian symptoms and akathisia (component II; maximum score, 78), dystonia (component III; maximum score, 48), and choreic movements (component IV; maximum score, 42), as well as the Clinical Global Impression of the severity of choreic movements (component V; maximum score, 8), parkinsonian symptoms (component VI; maximum score, 8), dystonia (component VII; maximum score, 8), and akathisia (component VIII; maximum score, 8). Limit lines indicate SEM. **P* < .01.

terior, had to have the lead reimplanted after 2 months (for this patient, the time to assessment was defined in terms of the time from lead reimplantation). In patient 1, a cable connection exerted painful traction, and the stimulator had to be fixed to the clavicle. In each case, the problem was fully resolved.

COMMENT

Continuous bilateral pallidal stimulation led to sustained improvement of motor symptoms in patients experiencing severe TD refractory to medical treatment. To our knowledge, this is the first assessment of the effects of DBS on TD in a prospective multicenter study with subsequent confirmation of the effects of stimulation by a double-blind evaluation after 6 months of treatment. To date, beneficial effects after pallidotomy^{14,15} and after pallidal stimulation¹⁶⁻¹⁹ have been reported in a few cases. In contrast to pallidotomy, pallidal stimulation has the advantage of the reversibility of its effects and offers the possibility of fine-tuning the electrical parameters to obtain the best level of improvement without inducing permanent adverse effects.

After 6 months of chronic stimulation, a clear improvement was obtained in all patients, as underlined by a decrease of more than 40% in the ESRS score and by global improvement considered to be major in each patient. Although it is too early to assess the chronic effects of stimulation, the improvement was observed at 3 months after surgery. Some variation in the degree of improvement (range, 40%-75% improvement of motor symptoms) was observed. The reasons for this variation are unclear. We found no association between patients' presurgical clinical characteristics (eg, age, psychiatric disorders, concomitant medication, and smoking history [2 patients were smokers]) and the efficacy of pallidal stimulation, but caution is needed in interpreting this finding in view of the small size of our series. Although there was no evidence of it on postoperative magnetic resonance imaging, we cannot rule out the possibility of slight variations in the final

location of the electrodes within the GPi, which might explain differences in efficacy among patients. Another potential reason for this variability is the heterogeneity of the disease, possibly in terms of the causal mechanisms (eg, the putative role of associated genetic factors, as this has been suggested to have a role in the variability of the effects of DBS for treating primary dystonia²⁹) but most notably in terms of the characteristics of the abnormal movements, which varied considerably among patients. However, beneficial effects were observed on dystonia and on the choreic component of TD and in upper limbs and lower limbs or axes, without significant differences in the degree of efficacy of GPi stimulation among the various types of movement. In line with the known beneficial effects of pallidal stimulation in Parkinson disease,⁹ the 6 patients with parkinsonism also had improvement of this antipsychotic-induced symptom. The improvement was marked, but parkinsonism was mild in these patients. The beneficial effects of chronic stimulation were demonstrated by a double-blind evaluation of the effects of stimulation at 6 months after surgery. All patients demonstrated worsening of the motor symptoms after the stimulation was turned off, an effect that was reversed when the stimulation was turned back on.

Lead implantation is not devoid of risks, with intracerebral hemorrhage and infection as the most serious potential adverse effects.³⁰ Moreover, DBS devices and stereotactic surgery are expensive. Therefore, such treatment should only be considered for patients with persistent (>1 year) severe and disabling TD refractory to medical treatment, with previous attempts at treatment with clozapine or tetrabenazine having proved ineffective. Psychiatric adverse effects, such as depression and behavioral disorders (including suicidality), have been reported in patients with parkinsonism treated by subthalamic stimulation³¹⁻³⁴ and in patients with primary dystonia treated by pallidal stimulation.³⁴ Having taken into consideration this putative risk, we carefully selected patients with resolved psychiatric disease (eg, nonpsychotic depression) or whose psychiatric condition was satisfactorily stabilized (ie, the absence of delirium, active delusion, or suicidal ideation) by antidepressant or antipsychotic drugs, and we monitored their psychiatric status. No serious psychiatric adverse effects were observed in this series of patients. Mood worsened in 3 patients. However, none of them met criteria for major depression, and they spontaneously improved during the subsequent 6 months (except for the use of antidepressant therapy in 1 patient). These mood changes might be similar to those observed in patients with parkinsonism and dystonia treated by DBS.³¹⁻³⁴ Their mechanism is putative and controversial. The primary explanations put forward are disappointment due to unrealistic expectations of the benefits of surgery, difficulty coping with a new life made possible by a marked improvement in motor condition, or the spread of DBS current to non-motor parts of the target nucleus or to adjacent structures.³⁴ In contrast, a patient in our study who had chronic depression, partly as a reaction to motor disability and social embarrassment due to TD, had an improvement in mood status after the disappearance of abnormal movements. Although the surgical procedure was well tolerated in the 4 patients with chronic psychosis, one cannot

exclude the risk of psychiatric decompensation in such patients. Strict selection criteria and close psychiatric monitoring are mandatory.

Pallidal stimulation seems to be an effective treatment for various abnormal movements, such as chorea in Huntington disease,¹² primary¹⁰ or secondary¹¹ dystonia, levodopa-induced dyskinesia in Parkinson disease,⁹ and (based on the present study) the choreic and dystonic components of TD. This suggests that these abnormal movements, despite different causes (eg, genetic origin or adverse drug effects), may share some common pathophysiological mechanisms. All of these movements might be associated with neural dysfunction at the level of the internal GPi. A reduced neuronal discharge rate and a change in the pattern of GPi neuronal activity have been observed in patients with parkinsonism experiencing dyskinesia induced by apomorphine hydrochloride (as in patients with chorea), as well as dystonia on intraoperative microrecordings performed during lead implantation for DBS treatment in these patients.³⁵ Although the mechanism of stimulation is not yet understood, it may act through the suppression of abnormal neural activity at this level and by the imposition of regular neural activity, albeit nonphysiological but less deleterious than the pathologic activity.³⁶ The subsequent normalization of the altered pallidal output may restore function of the subcortical cortical loops involved in motor control. Indeed, in patients having primary generalized dystonia and successfully treated by GPi DBS, a recent positron emission tomographic study³⁷ showed that the prefrontal overactivation associated with dystonia is reversed by effective GPi stimulation. Compared with subthalamic DBS for Parkinson disease, the amplitude and pulse width of stimulation were higher in the patients in the present study. Such settings are usual with pallidal DBS regardless of the disease being treated (ie, Parkinson disease⁹ and idiopathic dystonia¹⁰), and this is probably linked to the large size of the nucleus, which requires high-power stimulation to correct its neuronal dysfunction.

These results need to be confirmed in a larger group of patients with a longer follow-up. However, bilateral pallidal stimulation seems to offer a much-needed new treatment option for disabling TD.

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Author Contributions: Dr Damier had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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