Long-term neuropsychiatric outcomes after pallidal stimulation in primary and secondary dystonia

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ABSTRACT

Objective: To evaluate changes in the diagnosis of Axis I psychiatric disorders in patients with primary and secondary dystonia after deep brain stimulation (DBS) of the globus pallidus internus (GPi).

Methods: Structured Clinical Interviews for the *DSM-IV*, Axis I psychiatric disorders, were prospectively performed before and after surgery. Diagnoses were made based on *DSM-IV* criteria. Psychiatric disorders were grouped into 5 categories: mood, anxiety, addiction, obsessive-compulsive disorders, and psychosis. Patients could be stratified to more than one category. Rates for unchanged diagnoses, diagnoses in remission, and new-onset diagnoses after surgery for each category were calculated.

Results: Fifty-seven patients with primary and secondary dystonia were included. Mean $\pm$ SD age at surgery and dystonia duration at time of surgery was 50.6 ± 13.8 and 19.0 ± 13.2 years, respectively. Preoperatively, 37 Axis I diagnoses were made in 25 patients, 43.8% of those presenting with at least 1 Axis I diagnosis (mostly mood and anxiety disorders). Mean $\pm$ SD duration of psychiatric follow-up was 24.4 ± 19.6 months. Overall, after surgery no significant changes ($p = 0.16$) were found in Axis I diagnoses (23 patients, 40.3%): 27 (73%) unchanged, 10 (27%) in complete remission, and 4 (12.9%) new-onset diagnoses.

Conclusions: Our results support the overall psychiatric stability of patients with primary and secondary dystonia treated with GPi DBS. However, considering the high psychiatric morbidity in the dystonia population, psychiatric assessments before and after surgery are strongly recommended.

Classification of evidence: This study provides Class IV evidence that GPi DBS does not change Axis I psychiatric diagnoses in patients with primary and secondary dystonia. *Neurology*® 2015;85:433-440

GLOSSARY

BDZ = benzodiazepines; **BFMDRS** = Burke-Fahn-Marsden Dystonia Rating Scale; **CD** = cervical dystonia; **DBS** = deep brain stimulation; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; **GPi** = globus pallidus internus; **OCD** = obsessive-compulsive disorder; **SCID-I** = Structured Clinical Interview for the *DSM-IV* Axis I psychiatric disorders; **TWSTRS** = Toronto Western Spasmodic Torticollis Rating Scale.

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.¹ Psychiatric comorbidities, especially mood and anxiety disorders, are common in patients with dystonia.²⁻⁷ They are increasingly recognized as an important determinant of disability and quality of life.⁸⁻¹⁰ Deep brain stimulation (DBS) of the globus pallidus internus (GPi) has been shown to be effective in improving both motor severity and disability in patients with medication-refractory primary dystonia.¹¹⁻¹⁴ Nevertheless, the effects of DBS on the neuropsychiatric profiles of dystonic patients have not been well-investigated. One reason concerns the lack of detailed psychiatric assessments of these patients before and after DBS. Another reason is that patients with major and active psychiatric issues have frequently been excluded from studies examining long-term postoperative outcomes with reported results being mostly limited to patients without major

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psychiatric difficulties before surgery.^{13–19} However, 3 suicides have been reported so far within 14 months after bilateral GPi DBS.^{20,21} Moreover, studies reporting neuropsychiatric outcomes in various types of dystonia (primary generalized, cervical, and secondary dystonia) and in the long-term follow-up are lacking. Therefore, the neuropsychiatric consequences of GPi DBS on patients with dystonia in the short and long term remain unclear, as does the influence of active psychiatric disorders on the selection of appropriate candidates for the procedure.^{12–22}

We report the long-term impact of bilateral GPi DBS on the neuropsychiatric profiles of a population of patients with primary and secondary dystonia, assessed with the Structured Clinical Interview for the *DSM-IV* Axis I psychiatric disorders (SCID-I).²³

METHODS Primary research question. The primary research question was as follows: Does GPi DBS change Axis I psychiatric diagnoses in patients with dystonia? This study provides Class IV evidence that after GPi DBS, no significant changes ($p = 0.16$) occurred in Axis I diagnoses (23 patients, 40.3%) compared to before surgery (25 patients, 43.8%) in patients with primary and secondary dystonia.

Patients. Patients with primary and secondary dystonia who underwent bilateral GPi DBS surgery at the Toronto Western Hospital between November 1999 and November 2011 were included. Main selection criteria for DBS were as follows: (1) dystonia as main motor symptom; (2) lack of response to medical treatment (anticholinergics, benzodiazepines, tetrabenazine, botulinum toxin); (3) motor symptoms causing clinically significant distress or impaired function. Exclusion criteria were as follows: (1) active psychotic symptoms or active suicidal ideation; (2) medical contraindications for surgery (i.e., severe uncontrolled arterial hypertension, severe diabetes or cardiac disease, terminal cancer). Details of surgery and electrodes positioning in the GPi have been published elsewhere.²⁴

Psychiatric assessment. Patients were screened for psychiatric disorders preoperatively and postoperatively by 2 psychiatrists (M.Z., V.V.) trained in the use of the SCID-I. Diagnoses were made based on *DSM-IV* criteria. This evaluation allowed for the diagnosis of current Axis I psychiatric disorders and retrospective or lifetime diagnoses based on information provided by the patient, informants, and chart review.

The psychiatric findings were grouped into the following 5 principal categories:

1. Mood disorders: major depressive disorder, dysthymia, cyclothymia, bipolar affective disorder
2. Anxiety disorders: social anxiety, generalized anxiety disorder, panic attack with and without agoraphobia, specific phobias, anxiety disorder not otherwise specified, post-traumatic stress disorder
3. Addiction: alcohol and drug abuse/dependence
4. Obsessive-compulsive disorder (OCD)
5. Psychosis

Patients could be stratified to more than one category. Severity of symptoms and Global Assessment of Functioning were not used.

Rates for unchanged diagnoses, diagnoses in remission, and new-onset diagnoses after surgery for each category were calculated as follows: unchanged = (number of postoperative unchanged diagnoses/total number of preoperative diagnoses) $\times$ 100; remission = (number of postoperative diagnoses in remission/total number of preoperative diagnoses) $\times$ 100; new onset = (number of new postoperative diagnoses/total number of postoperative diagnoses) $\times$ 100.

The timing of the psychiatric follow-ups was personalized according to the needs of each patient. Patients' psychiatric history for major psychiatric disorders and medication changes were also noted.

Motor assessment. Patients with generalized/segmental dystonia were assessed and videotaped by a movement disorders neurologist (E.M.) before and after surgery using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS).²⁵ Patients with cervical dystonia (CD) were videotaped and assessed using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).²⁶ Regular follow-ups were scheduled at 6 months after surgery and once a year afterwards. Stimulator settings and medication changes were recorded at each visit. Motor outcome data were recorded from those assessments taking place closest in time to the last psychiatric visit available.

Outcome measures and statistical analysis. Primary outcome measure was the change in the total number of Axis I diagnoses after surgery compared to before surgery in the whole study population and in the 3 groups of dystonia. The Wilcoxon signed-rank test for paired samples was used to compare changes.

Secondary outcome measures were changes between before and after surgery in the BFMDRS and TWSTRS motor scores and in medication (at time of the last available psychiatric and motor follow-up) in each dystonia group. The Wilcoxon signed-rank test for paired samples was used for these analyses. Since patients were treated with different types of benzodiazepines (BDZ), we used the lorazepam equivalent daily dose²⁷ to compare BDZ treatment before and after surgery. Statistical analysis for changes in antidepressants, other dystonia medications, analgesics, and antipsychotics was not performed because of the wide heterogeneity of the drugs for each category.

Relative to the postoperative assessment, we defined a psychiatric outcome as stable when the Axis I diagnosis was unchanged, positive when the Axis I diagnosis went into complete remission, and negative when a new Axis I diagnosis was made or a suicide occurred.

The Mann-Whitney U test for continuous variables and the Fisher exact test for categorical variables were used to compare associated factors (sex; age; age at dystonia onset; age at psychiatric symptoms onset; dystonia group: primary CD, primary segmental/generalized, secondary; marital status; mean disease duration at surgery; motor scores change after surgery; previous suicidal ideation and suicide attempt; preoperative mood, anxiety, and addiction diagnosis; psychiatric history; family psychiatric history; preoperative medications: BDZ, antidepressants, antipsychotics, other antidystonia medications, analgesics) between (1) patients with stable or positive psychiatric outcome and patients with negative psychiatric outcome and (2) patients with previous history of suicide attempt and patients without previous history of suicide attempt. All statistical analyses were 2-sided, with a p value <0.05 considered significant.

Standard protocol approvals, registrations, and patient consent. The study was approved by the University Health Network Ethics Review Board. All patients consented to the use of their clinical records for the purpose of research.

Table 1 Clinical characteristics of the study population

Type of dystonia (no. of patients)	Sex, M/F	Age at dystonia onset, y	Age at psychiatric symptoms onset, y	Age at surgery, y	Duration of dystonia at surgery, y	Time between preoperative psychiatric assessment and surgery, mo	Psychiatric follow-up, mo	Motor follow-up, mo
Primary GEN/SEGM (26)	14/12	30.8 (19.4)	39.6 (13.2)	54.0 (19.4)	23.6 (15.4)	8.6 (5.4) [0.25-18]	21.8 (15.4) [3-67]	41.2 (26.3) [4-90]
Primary CD (20)	3/17	39.3 (12.6)	36.6 (17.0)	54.1 (10.3)	14.7 (14.2)	13.3 (6.0) [2-27]	28.3 (15.4) [11-60]	56.8 (33.8) [11-126]
Secondary (11)	2/9	17.1 (5.3)	18.3 (22.6)	36.8 (4.4)	19.4 (4.6)	10.1 (2.3) [1-24]	23.7 (9.8) [3-120]	37.3 (12.4) [8-156]
Total (57)	19/38	17.7 (19.1)	32.9 (11.4)	50.6 (13.8)	19.0 (13.2)	10.5 (6.3) [0.25-27]	24.4 (19.6) [3-120]	45.8 (66.8) [4-156]

Abbreviations: CD = cervical dystonia; GEN/SEGM = generalized/segmental dystonia.

Data are reported as mean (SD) [range] unless otherwise indicated.

RESULTS Patients. Of the 70 patients with dystonia who underwent GPi DBS, 57 (37 women, 20 men) were included in the study. Thirteen patients (8 women and 5 men; 10 primary dystonia and 3 secondary dystonia) were excluded because of incomplete psychiatric assessment before or after surgery. Of the 57 included patients, 20 had primary CD, 26 had primary generalized/segmental dystonia, including 3 genetic dystonia (2 with *DYT-1* mutation and 1 with *DYT-6* mutation), and 11 had secondary dystonia (5 generalized, 3 hemi, 3 segmental), of which 3 were poststroke, 2 dystonia-plus, 1 postencephalitis, 1 postanoxic, 1 posttraumatic, and 3 tardive (1 with psychosis and 2 with bipolar affective disorder, all treated with antipsychotics). The main characteristics of the study population are summarized in table 1.

Three women included in the study died: 1 after traumatic brain injury and 2 of suicide (one 29-year-old woman with posttraumatic segmental dystonia and one 50-year-old woman with generalized dystonia, at 2 years and at 4 years after surgery, respectively). Details about the 2 suicidal patients are available in appendix e-1 on the *Neurology*® Web site at Neurology.org.

History of psychiatric issues for each dystonia group is reported in table e-1. Main characteristics of patients with suicidal ideation, suicide attempts, and tardive dystonia are summarized in tables e-2 to e-4, respectively.

The electrical parameters of pallidal stimulation are reported in appendix e-1.

Primary outcomes. Before surgery, 25 (43.8%) patients met the diagnostic criteria for one or more Axis I diagnoses. Of these patients, 9 (15.8%) met diagnostic criteria for 2 or more Axis I diagnosis.

Mood disorders were diagnosed in 13 (22.8%) patients, anxiety disorders in 18 (31.6%), addiction in 4 (7.0%), OCD in 1 (1.7%), and psychosis in 1 (1.7%).

After surgery, 23 (40.3%) patients were diagnosed with one or more Axis I diagnosis, of whom 6 (10.5%) had 2 or more Axis I diagnosis (figure 1A). Ten (17.5%) patients met diagnostic criteria for mood disorders, 14 (24.6%) for anxiety disorders, 6 (10.5%) for addiction, 1 (1.7%) for psychosis, and none (0%) for OCD (figure 1B).

Overall, there were no changes in the number of Axis I diagnoses ($n = 31$) compared to before surgery ($n = 37$; $p = 0.16$). Specifically, 27 (73%) of Axis I diagnoses were unchanged, 10 (27%) were in complete remission, and 4 (12.9%) were new-onset diagnoses.

Preoperative and postoperative psychiatric assessments with changes in Axis I diagnoses in each dystonia group are detailed below and illustrated in figure 1C.

Primary generalized/segmental dystonia. After surgery, there was no difference ($p < 0.05$) between the total number of Axis I diagnoses ($n = 9$) compared to before surgery ($n = 13$). Specifically, 8 (61.5%) Axis I diagnoses were unchanged, 5 (38.5%) were in remission, and 1 (11.1%) was a new-onset diagnosis.

Primary CD. No differences ($p < 0.05$) were found between the total number of Axis I diagnoses after surgery ($n = 13$) compared to before surgery ($n = 14$). Postoperatively, 11 (71.4%) Axis I diagnoses were unchanged, 3 (21.4%) went into remission, and there were 2 (16.6%) new diagnoses.

Secondary dystonia. There were no differences ($p < 0.05$) between the postoperative ($n = 9$) and preoperative ($n = 10$) total number of Axis I diagnoses. Postoperatively, 8 (80%) Axis I diagnoses were unchanged, 2 (20%) were in remission, and 1 (11.1%) was a new-onset diagnosis.

Postoperative changes in each single psychiatric category (mood, anxiety, addiction, OCD, and psychosis) for the 3 groups of dystonia are detailed in figure 2.

Secondary outcomes. Motor outcomes. In primary generalized/segmental dystonia, there was a remarkable improvement ($p < 0.005$) of the BFMDRS motor

Figure 1 Axis I psychiatric diagnoses (A), Axis I psychiatric diagnoses distributed in the different categories (B), and Axis I psychiatric diagnoses according to dystonia classification (C)

(A) Patients with at least one Axis I psychiatric diagnosis or 2 or more Axis I psychiatric diagnoses before and after surgery in the study population. Numbers in the colored bars represent number of patients for each dystonia group. (B) Number of patients with Axis I psychiatric disorders divided by category (mood, anxiety, addiction, obsessive-compulsive disorder [OCD], and psychosis) before and after surgery. (C) Preoperative and postoperative psychiatric assessments with changes in Axis I diagnoses in primary generalized/segmental dystonia, primary cervical dystonia, and secondary dystonia. CD = primary cervical dystonia; GEN/SEGM = primary segmental and generalized dystonia; NS = *p* value not significant.

score after surgery (20.4 ± 22.7) compared to before surgery (31.9 ± 17.4); the disability score decreased ($p < 0.001$) from 8.4 ± 5.7 before surgery to 6.1 ± 6.0 after surgery.

In primary CD, there was a notable improvement in the TWSTRS severity score (from 23.1 ± 3.2 before surgery to 11.6 ± 4.9 ; $p < 0.001$ after surgery), in the disability score (from 17.5 ± 5.9 before surgery to 6.6 ± 6.7 after surgery; $p < 0.001$), and in the pain score (from 14.7 ± 4.1 before surgery to 7.5 ± 6.7 after surgery; $p < 0.005$).

In secondary dystonia, the BFMDRS motor scores improved (from 34.9 ± 22.1 before surgery to 23.8 ± 20.7 after surgery; $p < 0.005$); there were no changes in the disability scores.

Medication changes. Data about medication changes in each dystonia group are available in table e-5 and detailed in appendix e-1.

Psychiatric outcomes and associated factors. None of the examined factors was found to be associated with stable or positive psychiatric outcome compared to negative outcome in the dystonia population (table e-6).

Figure 2 Axis I psychiatric diagnosis categories allocated to dystonia classification

Postoperative changes in each psychiatric category (mood, anxiety, addiction, obsessive-compulsive disorder [OCD], and psychosis) in primary generalized/segmental dystonia (GEN/SEGM), primary cervical dystonia (CD), and secondary dystonia. Values in the colored bars are expressed as number of patients with each single Axis I diagnosis. Bar-sided values for each row are expressed as sum of values (%) in the colored bars. AA = alcohol abuse; AD = alcohol dependence; BAD = bipolar affective disorder; DA = drug abuse (cannabis); GAD = generalized anxiety disorder; MDD = major depressive disorder; NB = nail biting; NOS = anxiety disorder not otherwise specified; P = panic disorder; PH = phobia; PTSD = post-traumatic stress disorder; SA = social anxiety; SCZ = schizoaffective disorder. ^aTardive dystonia. ^bSituational phobia (driving). ^cSocial phobia.

Comparing patients with a history of suicide attempt ($n = 7$) to nonattempter patients ($n = 48$), the former were associated with younger onset of psychiatric symptoms (30.7 ± 11.4 years vs 41.1 ± 14.3 years; $p = 0.011$), psychiatric history ($7/7$ vs $30/50$; $p = 0.038$), having preoperative anxiety ($4/7$ vs $10/50$; $p = 0.033$), and addiction ($2/7$ vs $2/50$; $p = 0.017$).

DISCUSSION This study reports novel findings on the long-term neuropsychiatric outcomes using psychiatric interviews and *DSM-IV* diagnostic criteria in patients with primary and secondary dystonia and GPi DBS. Most Axis I diagnoses (73%) made before surgery did not change (particularly, there was no worsening) after GPi DBS and 24.3% of them completely resolved after surgery. These results strongly support the safety of this surgery and a possible beneficial role of pallidal stimulation on the neuropsychiatric profile of patients with dystonia, particularly those with mood disorders. There was no association between positive psychiatric history and postoperative negative psychiatric outcome. Notably, bilateral GPi DBS was safe in dystonic patients with a history of major psychiatric illness.

The few available studies reporting on neuropsychiatric outcomes after GPi DBS have showed some improvement in mood and no major change in anxiety in primary dystonia^{13–16,18,28,29} and more variable outcomes in secondary dystonia.^{17,30,31} These reports have been limited by the small sample size, the relatively short follow-up (≤ 36 months), and the lack of use of psychiatric interviews to assess patients.

In our primary generalized/segmental dystonia population, mood disorders showed a trend to improvement after DBS (figure 2), similarly to published studies.^{15,18,28,29,32} This improvement could be secondary to the GPi DBS motor benefit, and the consequent reduction in disability and improvement of quality of life.³² In our population, the postoperative reduction of pain could also have contributed to improve depression.

Moreover, the discontinuation of tetrabenazine because of the motor benefit after surgery might have played a role in the improvement of depressive symptoms in a few cases (table e-5; appendix e-1).

A possible direct effect of pallidal stimulation cannot be excluded, as it has been suggested in patients with Tourette syndrome³³ and patients with Parkinson disease treated with GPi DBS,³⁴ based on the hypothesis of the possible spread of stimulation current from the motor area to the limbic structures of the GPi.

The relative stability of anxiety disorders in primary generalized/segmental dystonia (figure 2) is consistent with previous studies.^{13,15} Of note, in our population anxiety disorders remained stable even after BDZ reduction or discontinuation after surgery (table e-5). Pallidal stimulation was beneficial for OCD (nail biting) in one of our primary generalized/segmental dystonia patients, in contrast with previous data in myoclonus-dystonia,³⁵ likely related to a possible psychiatric vulnerability of this genetic form of dystonia.³⁶

In our patients with primary CD, mood disorders and anxiety disorders were overall stable after surgery (figure 2). However, the occurrence of one episode of anxiety after successful surgery likely due to the rapid withdrawal of BDZ and resolved by BDZ therapy resumption supports the hypothesis that postoperative exacerbation of anxiety disorders in some cases might be related to withdrawal of BDZ.⁵

Similarly, in our patients with secondary dystonia, anxiety disorders remained stable after surgery, despite the BDZ reduction, with some improvement in a few patients (figure 2). Our 3 patients with tardive dystonia showed stable psychiatric outcome, providing further evidence about the long-term safety of GPi DBS on mood and psychotic symptoms in this particular population.^{17,31,32,37}

The effect of GPi DBS on addictive behavior remains uncertain. Cannabis abuse in one patient with secondary dystonia remained unchanged after surgery. There was also a recurrence of addictive behavior (alcohol) in another 2 patients whose symptoms were in full sustained remission prior to surgery.

Interestingly, we found a high prevalence of suicidal ideation ($n = 7$, table e-2) and attempted suicide ($n = 7$, table e-3) in the psychiatry history of our patients. However, prevalence studies of suicidal ideation and suicide attempts in patients with dystonia are lacking. Factors associated with a history of suicide attempt in our study are in keeping with the general population.³⁸ We did not find that a preoperative history of suicidal ideation or suicide attempt was associated with negative psychiatric outcome. Nevertheless, we did have 2 cases (3.5%) of completed suicide after successful pallidal stimulation. This adds to the previous literature of suicide in 2 patients with primary dystonia and one with post-nocic dystonia, treated with DBS.^{20,21} All 3 cases were male, had a preoperative history of depression, and completed suicide within the first 14 months after DBS. Risk factors for suicide in the dystonic population following DBS surgery are relatively unknown. Male sex and multiple surgical procedures for dystonia have been suggested as possible risk factors.⁵ This is out of keeping with our cases, both female, with DBS being the only surgical intervention. Our data do not support a direct association between DBS surgery and suicide in our 2 patients. The temporal interval between surgery and suicide was long (2 and 4 years, respectively) and the stimulation parameters were not changed close to the suicides, thus excluding a possible acute effect of pallidal stimulation on mood.³⁴

There are no available data for establishing the exact duration of a temporal window in patients with dystonia with psychiatric disorders before

considering safe their candidacy to DBS surgery. We made a collegian decision to establish a window of at least 6 months (or more according to the patient) of stable psychiatric condition before considering surgery.

We confirmed the long-term efficacy of pallidal stimulation in improving motor symptoms in primary dystonia.^{11,14,39,40} GPi DBS was less effective in secondary dystonia, as expected.^{17,30,31,37}

Our study has several limitations. Individual follow-up times were variable. The etiologic heterogeneity of our population might have some impact on the results. Psychiatric data were not available for all patients who therefore had to be excluded. Severity of psychiatric symptoms was not assessed, so that some worsening could not be captured by our data.

Our study supports the psychiatric safety of pallidal stimulation in dystonia, even in patients with a history of major psychiatric issues. Although our results were limited by the small sample size, none of the preoperative neuropsychiatric symptoms was associated with a negative psychiatric outcome, suggesting that previous and current major psychiatric illnesses should not be considered as absolute contraindications to surgery in primary and secondary dystonia candidates for GPi DBS.

Nevertheless, considering the frequent psychiatric morbidity and the high risk of suicide in the dystonia population, psychiatric assessment before and after surgery is strongly recommended.

Further studies involving larger and more homogeneous patient samples are needed to confirm our results.

AUTHOR CONTRIBUTIONS

Sara Meoni: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, statistical analysis. Mateusz Zurowski: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, statistical analysis, study supervision. Andres M. Lozano: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, study supervision, obtaining funding. Mojgan Hodaie: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data. Yu-Yan Poon: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data. Melanie Fallis: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, acquisition of data. Valerie Voon: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Elena Moro: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision.

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