Efficacy and Safety of Deep Brain Stimulation in Patients With Medication-Induced Tardive Dyskinesia and/or Dystonia: A Systematic Review

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ABSTRACT

Background: Tardive dyskinesia and dystonia (TDD) are severe side effects of dopamine-blocking agents, particularly antipsychotics. While deep brain stimulation (DBS) has proven effective in the treatment of TDD, little is known about the possible psychiatric complications of DBS in psychiatric patients.

Objective: To assess the efficacy and safety, specifically the psychiatric side effects, of DBS in patients with medication-induced TDD.

Data Sources: PubMed and EMBASE databases were searched systematically on May 25, 2011, for articles written in English, using the search terms *deep brain stimulation* AND *tardive*.

Study Selection: Of the 88 original articles retrieved, 17 studies involving 50 patients with TDD who underwent DBS were included in the review.

Data Extraction: Data on the severity of the movement disorders before and after DBS, as rated on the Burke-Fahn-Marsden Dystonia Rating Scale or similar scales, were extracted. Data on psychiatric symptoms before and after DBS were used to calculate the percent improvement per patient per rating scale. Overall improvement and confidence intervals were calculated using a 1-sample, 2-sided Student *t* test.

Results: The mean improvement of TDD of the combined patients 3 to 76 months after implantation was 77.5% (95% CI, 71.4%–83.3%; $P < .000$) on the Burke-Fahn-Marsden Dystonia Rating Scale. Of the 50 patients, 1 experienced an exacerbation of depression, and 1 experienced an exacerbation of psychosis.

Conclusions: DBS seems to be effective and relatively safe for patients with treatment-resistant TDD; however, the results should be interpreted with caution, as most of the data are from case reports and small trials.

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Medication-induced tardive dyskinesia and tardive dystonia (TDD) are characterized by twisting or jerking movements that typically occur after long-term treatment with dopamine-blocking agents, mostly antipsychotics,[1] but also with certain antiemetics (metoclopramide and prochlorperazine) and antidepressants.[2] The prevalence of tardive dyskinesia in patients treated with antipsychotics ranges from 32.4% for first-generation antipsychotics to 13.1% for second-generation antipsychotics,[3] while the prevalence of tardive dystonia ranges from 0.4%–9%,[4] depending on the population and type of antipsychotic used. Both conditions may occur in the same patient.[1] Tardive syndromes, especially when dystonic features are present, can become socially or even physically disabling or painful. The most recent Cochrane review[4] did not find sufficient evidence from randomized controlled trials to support one specific treatment option, although there was some evidence from other types of studies that the following treatment strategies may provide benefit: lowering the dosage or stopping antipsychotics, switching to clozapine or another second-generation antipsychotic, or adding tetrabenazine.[4] For dystonia, particularly focal dystonia, injections of botulinum toxin may be helpful.[1] Unfortunately, some patients with severe forms of TDD do not benefit from pharmacologic interventions,[1,3,5] even after the offending medication has been discontinued.[4,6,7]

Deep brain stimulation (DBS) is a surgical technique that has been successfully used to treat movement disorders such as Parkinson's disease, tremor, and primary dystonia,[8–11] although results are less clear-cut for secondary dystonia (eg, after traumatic brain injury and cerebrovascular accidents).[12] Preliminary research indicates that patients with TDD benefit from DBS,[8,11,13–15] whereas patients with other forms of secondary dystonia do not.[8] Moreover, clinicians may be reluctant to use DBS, not only because of the lack of evidence for randomized controlled trials supporting its effectiveness, but also because it might give rise to psychiatric side effects in patients who already have psychiatric problems and because it requires clinicians to change their mindset and seek a surgical rather than medical solution.[16] Most studies of DBS excluded patients with a history of severe depression or "major psychiatric disorders"[17] because of the presumed high risk of psychiatric side effects such as manic symptoms, depression, impulse-control problems, and attempted suicide, which had been observed in some patients with Parkinson's disease after electrode implantation.[18,19] However, the subthalamic nucleus is usually stimulated in patients with Parkinson's disease, a site that is associated with a higher risk of psychiatric side effects than is the globus pallidus internus (GPi), the most common stimulation target in TDD.[18–20]

The goal of this systematic review was to evaluate the efficacy of DBS in the GPi on medication-induced TDD and the risk of psychiatric complications.

METHOD

Search Strategy

On May 25, 2011, the PubMed and EMBASE databases were searched, using the search terms *deep brain stimulation* AND *tardive*, with the limitations that studies must involve humans and be written in English (PubMed) and must be

original articles (EMBASE). No date limitations were used. The references of retrieved articles were also screened. For inclusion, studies had to report the severity of the movement disorders before and after DBS electrode implantation, measured in individual patients by means of rating scales.

In total, 112 articles were identified, of which 88 remained after duplicates were excluded. A further 66 articles were excluded because (1) the patients did not have medication-induced TDD (19 articles), (2) DBS was not the intervention treatment (16 articles), (3) the article was a review (30 articles), or (4) the stimulation target was not the GPi (1 article). The full text of the remaining 22 articles was reviewed, which led to the exclusion of a further 5 articles that did not match our inclusion criteria. Two other articles were identified from the reference lists, so that 17 articles were included (Table 1).

To ensure that the same patient was not entered more than once in multiple publications by the same author group, patient data regarding date of birth, ages at onset, and symptom ratings were compared. As noted in Table 1, 3 patients were published twice, in both Gruber et al[14] and Trottenberg et al.[32] Another patient was included twice because the patient had undergone 2 separate procedures: in 1 report,[30] the stimulation leads had stopped functioning, and in the other,[21] the stimulation leads had been reimplanted.

Statistical Analysis

Data were retrieved on TDD severity (Burke-Fahn-Marsden Dystonia Rating Scale [BFMDRS], Abnormal Involuntary Movement Scale [AIMS], and Extrapyramidal Symptom Rating Scale [ESRS]) before and after DBS and, if available, on age at onset of TDD, duration of TDD symptoms, age at surgery, gender, psychiatric diagnosis, psychiatric and nonpsychiatric side effects, rating scale used, duration of follow-up, DBS target, study funding, and study design. Individual data for all patients are available from the corresponding author on request.

The improvement per patient was calculated as a percentage per rating scale. SPSS version 18.0 was used for data analysis; all scores showing improvement were squared, and the subsequent data were checked for normal distribution. The overall improvement and confidence intervals were calculated using a 1-sample, 2-sided Student *t* test to obtain a mean improvement score and a 95% confidence interval (CI). The effect of patient characteristics on changes in BFMDRS total score was evaluated with a Pearson coefficient when possible. When assumptions of linearity were violated, a Spearman ρ was used (age at surgery, age at onset, duration of symptoms, and duration of follow-up). A χ^2 test was used for categorical variables (gender, diagnosis, DBS target, funding, and study design). The *P* value indicating significance was set at < .01 for all tests.

RESULTS

Table 1 shows the characteristics of the patients. Of the 50 patients included in this review, 44 had a known psychiatric diagnosis, and 1 had antiemetic-induced TDD; for 5 patients, no psychiatric diagnosis was reported. Presurgery psychotic symptoms were scored on the Positive and Negative Syndrome Scale (PANSS) in 10 patients[13]; mood symptoms were scored on the Montgomery-Asberg Depression Rating Scale (MADRS) for 19 patients[13,14] and on the Beck Depression Inventory (BDI) for 3 patients.[28] Some of the studies required patients to have had a stable psychiatric status for at least 6 months.

Clinical Points

- Deep brain stimulation is an effective and relatively safe treatment for severe tardive dyskinesia and/or dystonia.
- Deep brain stimulation should be considered an option for treatment-resistant severe tardive dyskinesia and/or dystonia.

Motor Improvement

On the BFMDRS, the mean improvement in the movement and disability subscale scores and the total score was 80.9% (95% CI, 74.7%–86.6%), 74.0% (95% CI, 65.0%–83.3%), and 77.5% (95% CI, 71.4%–83.3%), respectively (all $P < .000$). The same significant ($P < .000$) improvement was seen in the AIMS and ESRS scores, with an average improvement on the AIMS of 71.5% (95% CI, 62.6%–79.3%) and on the ESRS of 67.2% (95% CI, 55.5%–77.2%).

Effect of Covariates on Motor Improvement

None of the *P* values found were significant. The lowest *P* value was .07 for age at surgery. All other covariates reported in the method sections were much higher.

Psychiatric Side Effects

In 12 patients, the presence or absence of psychiatric side effects after the operation was not specifically mentioned in the studies.[9,22,25–27,31,33] In 10 of the 50 patients, 1 of whom was included twice,[21,30] for whom the presurgery and postsurgery ratings on the PANSS and the MADRS were reported, no significant overall presurgery versus postsurgery difference was found.[13] Other studies reported significant mood improvement on the MADRS (9 patients)[14] and the BDI (2 patients).[28] The publications containing the remaining 17 patients reported on psychiatric side effects without the use of a rating scale.[10,21,23,24,29,32]

One patient with previous depressions developed another depressive episode within a year of the surgery,[13] and 1 patient with schizophrenia had a psychotic relapse 6 months after surgery.[32]

Nonpsychiatric Side Effects

One patient had a cerebral infarction in the premotor cortex and thus did not benefit from DBS, although his symptoms did not become markedly worse, either.[22] Many patients

Table 1. Characteristics of Studies Included in the Review of Psychiatric Complications of Deep Brain Stimulation

Study	No. of Patients	Motor Scale	Type of Blinding	Psychiatric Inclusion Criteria and Psychiatric Rating Scales Used
Capelle et al, 2010[21]	4	BFMDRS	None	No history of major psychosis, antipsychotics discontinued
Chang et al, 2010[22]	5	BFMDRS, ESRS	Preoperative and postoperative video[a]	Antipsychotics discontinued
Cohen et al, 2007[23]	2	BFMDRS	None	…
Damier et al, 2007[13]	10	ESRS, AIMS	Stimulation on/off[b]	Stable psychiatric symptoms for 12 mo Rating scales: PANSS, MADRS
Eltahawy et al, 2004[24]	1	BFMDRS	None	…
Franzini et al, 2005[25]	2	BFMDRS	None	…
Gruber et al, 2009[14]	9[c]	BFMDRS, AIMS	None	No acute psychiatric symptoms or severe depression in the last 6 mo Rating scale: MADRS
Kefalopoulou et al, 2009[26]	1	BFMDRS, AIMS	Stimulation on/off[b]	Controlled psychiatric condition
Kosel et al, 2007[27]	1	BFMDRS	None	…
Krause et al, 2004[28]	3[d,e]	BFMDRS	None	Rating scale: BDI
Magariños-Ascone et al, 2008[9]	1[d]	BFMDRS	None	Absence of psychiatric disturbances
Pretto et al, 2008[10]	1[d]	BFMDRS, AIMS	Preoperative and postoperative video[a]	…
Sako et al, 2008[29]	6	BFMDRS	None	…
Schrader et al, 2004[30]	1[f]	AIMS	Stimulation on/off[b]	…
Trottenberg et al, 2001[31]	1	BFMDRS, AIMS	Stimulation on/off[b]	…
Trottenberg et al, 2005[32]	5[c]	BFMDRS, AIMS	None	…
Yianni et al, 2003[33]	1[d]	BFMDRS, AIMS	None	…

[a]Ratings were performed via videotaped examinations by a neurologist blinded to preoperative versus postoperative status.
[b]Rater was blinded to whether stimulation was turned on or off.
[c]Three patients were published twice, in both Gruber et al[14] and Trottenberg et al.[32]
[d]These studies included many different forms of dystonia/dyskinesia; patients with medication-induced tardive dyskinesia and dystonia were extracted for the review.
[e]One patient excluded because follow-up data were not available.
[f]Unilateral implant. Patient later included in Capelle et al[21] after implantation of new device.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BDI = Beck Depression Inventory, BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale, ESRS = Extrapyramidal Symptom Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale. Symbol: … = no psychiatric inclusion criteria or psychiatric rating scales mentioned.

had temporary side effects during calibration of the stimulation parameters, and these resolved after the stimulation settings were adjusted. Lasting somatic or implant-related side effects were chest battery infection (2 patients),[22,31] lead reimplantation (1 patient),[13] and adjustment of lead tension (1 patient).[13] One case study reported the loss of 1 electrode and less dexterous hand movements.[30]

DISCUSSION

This systematic review shows that DBS greatly improves motor scores in patients with TDD and that the reported, but not systematically assessed, psychiatric side effects are limited. Although based on limited evidence that is not always from randomized controlled trials, this review suggests that DBS is a clinically relevant treatment option for patients with severe TDD who do not respond to or cannot tolerate pharmacologic interventions. This conclusion is in line with earlier reviews.[12,34]

To our knowledge, this is the first review to address the psychiatric side effects of DBS in patients with TDD. Unfortunately, most of the studies included in the review did not systematically measure the patients' psychiatric status before and after DBS, and therefore findings might be biased. Of the 44 patients with a psychiatric diagnosis before DBS, only 2 (5%) experienced an exacerbation of their symptoms, and no patients developed new symptoms. If DBS were truly dangerous to the psychiatric health of patients with TDD, one would expect more reports of psychiatric exacerbations and new symptoms. This finding is consistent with a recent review by Jahanshahi et al,[35] which found no evidence that patients with primary dystonia or TDD with severe depression suffered from negative psychiatric effects after DBS of the GPi. A possible explanation for these minimal psychiatric side effects compared with those seen after DBS in patients with Parkinson's disease is the difference in stimulation site, namely, the GPi in patients with TDD and the subthalamic nucleus in patients with Parkinson's disease.[18–20]

One review[12] found fewer symptoms and a shorter duration of symptoms before DBS to be independent predictors of improved motor scores after DBS. Our review found various covariates not to affect the outcome, with the lowest *P* value being .07 for age at surgery and age at onset. This lack of effect of covariates might be because a low *P* value (< .01) was used to indicate significance. The *P* value would have been even lower if a Bonferroni correction had been applied (.005 significant *P* value, .010 trend *P* value); however, this would have been inappropriate given the small sample size and low power of the review.

Limitations

This review had a number of limitations that should be considered. For example, publication and observer bias are potentially present in this type of review. Many of the studies included were case reports, which are prone to publication bias, and no effort was made to blind either the clinician

Table 2. Patient Demographics, Symptoms Before and After Deep Brain Stimulation, and Psychiatric Characteristics

	Nonaffective Psychosis		Affective Psychosis		Other Diagnosis		Total	
	Median (SD)	n (%)	Median (SD)	n (%)	Median (SD)	n (%)	Median (SD)	n (%)
Patients		10 (20)		27 (54)		13 (26)		50 (100)
Sex								
Male		7 (70)		7 (26)		5 (38)		19 (38)
Female		3 (30)		20 (74)		8 (62)		31 (62)
		n		n		n		n
Age at surgery, y	37 (14.4)	10	48 (11.9)	27	55 (16.4)	13	48 (14.4)	52
Age at TDD onset, y	34 (14.9)	8	44 (12.9)	22	62 (18.9)	8	44 (15.0)	38
Time with TDD symptoms, y	5 (2.7)	8	5 (4.2)	22	4 (2.8)	8	5 (3.6)	38
Follow-up time, mo	10 (24)		16 (15)		12 (12)		12 (16)	
BFMDRS total								
Preoperative	36 (14)	7	46 (31)	20	48 (25)	13	43 (27)	39
Postoperative	5 (7)	7	6 (26)	20	16 (21)	13	8 (22)	39
BFMDRS movement								
Preoperative	25 (10)	6	33 (28)	17	36 (20)	9	33 (23)	31
Postoperative	3 (5)	6	3 (20)	17	9 (8)	9	5 (16)	16
BFMDRS disability								
Preoperative	8 (6)	6	9 (6)	17	9 (6)	9	9 (6)	31
Postoperative	1 (4)	6	1 (6)	17	4 (4)	9	2 (5)	31
AIMS								
Preoperative	25 (8)	6	24 (7)	14	22 (10)	5	24 (7)	24
Postoperative	6 (8)	6	9 (6)	14	5 (4)	5	6 (6)	24
ESRS total								
Preoperative	63 (59)	4	56 (36)	10	31 (NA)	1	39 (41)	15
Postoperative	19 (25)	4	22 (15)	10	16 (NA)	1	21 (17)	15

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale, ESRS = Extrapyramidal Symptom Rating Scale, NA = not applicable, SD = standard deviation, TDD = tardive dyskinesia and tardive dystonia.

(rater) or the patient. To assess for publication bias and observer bias, the studies were scored for blinding and for being part of a larger patient series or study. Neither had an effect on the improvement in motor scores. The psychiatric status of patients before and after DBS was seldom systematically assessed, which could have resulted in reporting bias.

Another potential limitation is that results for tardive dyskinesia and tardive dystonia were not reported separately, but this is probably not a problem, because most patients suffer from both conditions. Also, different motor assessment scales were used (BFMDRS, AIMS, and ESRS), and the duration of follow-up varied widely between studies, ranging from 3 to 76 months; however, covariate analysis showed that the duration of follow-up did not significantly affect motor scores ($P = .20$).

Of the 50 patients included in the review, 5 had no known psychiatric diagnosis, and 1 developed TDD after using dopamine-blocking antiemetics. It is possible that these patients responded differently to DBS than patients with a psychiatric diagnosis; however, exclusion of these patients did not significantly change the improvement in motor scores.

Most patients who developed TDD received antipsychotic treatment for affective disorders with psychotic symptoms (Table 2), and only 20% were treated for a nonaffective psychosis. This diagnostic distribution may have been due to selection bias, because some studies used a stable psychiatric status for at least 6 months as an inclusion criterion.[13,22,23] Another possibility is that patients with a history of an affective psychiatric disorder are more likely to complain about their movement disorder than patients with schizophrenia, who often suffer from cognitive and negative symptoms. There was no evidence that the patients' diagnosis had an effect on the motor improvement seen after DBS ($P = .57$).

In conclusion, our results indicate that DBS is effective in treating TDD in psychiatric patients and gives rise to few psychiatric side effects. The potential risk of publication and observer bias due to the nature of the papers included means that findings should be interpreted with caution.

Drug names: clozapine (Clozaril, FazaClo, and others), metoclopramide (Reglan and others), prochlorperazine (Compro and others), tetrabenazine (Xenazine).

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