Deep Brain Stimulation Results in Greater Symptomatic Improvement in Tourette Syndrome than Conservative Measures: A Meta-Analysis

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Keywords

Tourette syndrome (TS) · Deep brain stimulation (DBS) · Yale Global Tic Severity Scale (YGTSS) · Habit reversal training (HRT) · Meta-analysis

Abstract

Introduction: Deep brain stimulation (DBS) has emerged as a safe and effective therapy for refractory Tourette syndrome (TS). Recent studies have identified several neural targets as effective in reducing TS symptoms with DBS, but, to our knowledge, none has compared the effectiveness of DBS with conservative therapy. **Methods:** A literature review was performed to identify studies investigating adult patient outcomes reported as Yale Global Tic Severity Scale (YGTSS) scores after DBS surgery, pharmacotherapy, and psychotherapy. Data were pooled using a random-effects model of inverse variance-weighted meta-analysis ($n = 168$ for DBS, $n = 131$ for medications, and $n = 154$ for behavioral therapy). **Results:** DBS resulted in a significantly greater reduction in YGTSS total score ($49.9 \pm 17.5\%$) than pharmacotherapy ($22.5 \pm 15.2\%$, $p = 0.001$) or psychotherapy ($20.0 \pm 11.3\%$,

$p < 0.001$), with a complication (adverse effect) rate of 0.15/case, 1.13/case, and 0.60/case, respectively. **Conclusion:** Our data suggest that adult patients with refractory TS undergoing DBS experience greater symptomatic improvement with surprisingly low morbidity than can be obtained with pharmacotherapy or psychotherapy.

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Introduction

Gilles de la Tourette syndrome, also known as Tourette syndrome (TS), is a disorder characterized by spasmodic motor behaviors and vocalizations known as tics [1]. Current treatment for TS includes pharmacological, behavioral and, rarely, surgical therapy [2]. Initial behavioral therapy aims to reduce tics via behavior modification, and the most common modality is habit reversal training (HRT; interrupting tics with physically compet-

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ing responses so that the tic is no longer part of a chain of movements) [2].

The most commonly prescribed medications include α -adrenergic agonists, benzodiazepines, antipsychotics, and botulinum toxins [2–4]. Although some studies suggest that certain drugs may be more effective, such as antipsychotics, clonidine, guanfacine, and baclofen, there is no universally accepted standard therapy [5] and new trials of drug candidates are frequent [6]. Currently, 3 medications (haloperidol, pimozide, and aripiprazole) have FDA approval to treat TS; they have limited efficacy in severe forms of TS and can be associated with undesirable side effects [3].

Recently, several groups have investigated the effectiveness of deep brain stimulation (DBS) for patients with treatment-refractory TS [3, 7]. Studies have shown a correlation between decreased caudate nucleus volumes and tic severity as well as diminished connectivity between the caudate nucleus and the lateral frontal cortex [7], suggesting that abnormal signaling is associated with cortical disinhibition and results in involuntary, repetitive movements such as tics [7]. DBS is theorized to alleviate the underlying abnormal circuitry by manipulating these circuits [8]. Initial trials by Ackermans et al. [9] in 1999 targeted the centromedian and ventral oral internal thalamic nuclei and the substantia periventricularis. Recently, common targets have included the thalamus and globus pallidus pars interna, based on the theory that abnormal basal ganglia-thalamo-cortical loops underlie TS [7].

Previous reviews of DBS efficacy in TS have demonstrated improvement of both motor and vocal symptoms; however, the studies analyzed were primarily case reports or small case series with variable methodology. In this meta-analysis, we analyze published trials and case series from the pharmacological, psychotherapy, and DBS literature to compare the effectiveness of these therapeutic modalities in reducing the symptoms of TS.

Methods

Literature Search

PubMed and Embase searches were performed for English articles published between 1992 and 2017, defining an arbitrary 15-year window. For the behavior arm, search terms were “tourette behavior habit reversal training,” and articles were also taken from 4 previous literature reviews [10–13]. For the medication arm, search terms were “tourette medicine” and “tourette drug” with a clinical trials filter. For the DBS arm, studies used in a previous review article [14] were screened, and a search was performed using the same terms (“Tourette’s syndrome OR Tourette syndrome OR Gilles de la Tourette syndrome OR Tourette’s disorder OR Tourette OR tic disorder” and “deep brain stimulation OR DBS”) to

obtain articles published after March 2013. Studies were excluded if they were single-case reports, had participants with a mean age <16 years, or did not include Yale Global Tic Severity Scale (YGTSS) data.

Our analysis was specifically designed to include 3 patient cohorts that are directly comparable. TS is, by definition, a childhood-onset disorder, and symptoms usually resolve by adulthood. By restricting our analysis to adults, we studied only the subset of patients in whom the disease is chronic and resistant.

Data Collection and Management

Data extracted from each article included, where available, numbers of cases, pre- and posttreatment YGTSS scores (total and components), demographics (mean age, symptoms duration, and length of follow-up) and adverse events associated with treatment. In series employing DBS, stereotaxic targets were also reported. Other scores, such as the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Beck Depression Inventory (BDI), and State Trait Anxiety Inventory (STAI) scores, were also tabulated when reported.

Tic severity is often measured using the YGTSS, which assesses number, frequency, intensity, complexity, and interference with actions or speech for both motor and phonic or vocal tics [15]. This subtotal is combined with an impairment score to provide a global score, referred to as YGTSS total. Pooled mean baseline YGTSS total and response to treatment was determined using a random-effects, inverse variance-weighted meta-analysis of observational data [16], as were mean age, duration of symptoms, length of follow-up, and incidences of individual complications. Relation of YGTSS total to follow-up duration was determined for each treatment modality with the aid of meta-regression [17]. This study adhered to the guidelines set forth by the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group [18]. Calculations of model outputs employed beta distributions of probabilities and utilities.

Analysis

The primary analysis involved comparing the impact of each treatment on YGTSS total, using the percentage improvement in YGTSS total from baseline to follow-up. Secondary analyses involved comparing incidences of adverse events and values of demographic variables. Statistical comparisons employed the Student *t* test (2 variables) and ANOVA with the Bonferroni correction for multiple measures (≥ 3 variables). An ANCOVA test, using a mixed-effects meta-regression model, was then used to control for any demographic covariates significantly different between the treatments [19]. The Pearson and Spearman tests were also performed to examine any correlations between YGTSS improvement and age, and YGTSS improvement and baseline scores among studies. Differences whose probabilities were <5% were considered significant. We used Stata software (v12.1, StataCorp, College Station, TX, USA) to perform meta-analytical pooling, meta-regression, and statistical analysis.

Results

We reviewed 38 behavioral studies, 145 pharmacotherapy studies, and 163 DBS studies. After applying exclusion criteria, a total of 2 behavioral, 6 medication, and 21 DBS

Table 1. Studies included in the meta-analysis [25, 29–35, 38, 41–59]

First author [ref.], year	Title (first 4 words)	Cases, <i>n</i>	Treatment
Dehning [41], 2011	Globus pallidus internus-deep brain	3	DBS
Dehning [42], 2014	Functional outcome and quality	6	DBS
Dong [43], 2012	Unilateral deep brain stimulation	2	DBS
Dowd [33], 2018	Deep brain stimulation for	13	DBS
Huys [44], 2016	Motor improvement and emotional	8	DBS
Kaido [45], 2011	Deep brain stimulation for	3	DBS
Kefalopoulou [31], 2015	Bilateral globus pallidus stimulation	15	DBS
Kuhn [46], 2012	In vivo evidence of	2	DBS
Maciunas [47], 2007	Prospective randomized double-blind trial	5	DBS
Marceglia [48], 2010	Thalamic single-unit and local	7	DBS
Martinez-Fernandez [32], 1997	Deep brain stimulation for	5	DBS
Motlagh [49], 2013	Lessons learned from open-label	8 ^a	DBS
Nair [50], 2014	The anteromedial GPi as	4	DBS
Okun [51], 2013	A trial of scheduled	5	DBS
Porta [52], 2012	Deep brain stimulation for	18	DBS
Sachdev [53], 2014	Deep brain stimulation of	17	DBS
Savica [54], 2012	Deep brain stimulation in	3	DBS
Servello [55], 2009	De novo and rescue DBS	4 ^a	DBS
Welter [56], 2017	Anterior pallidal deep brain	16	DBS
Zhang [34], 2016	Deep brain stimulation of	24	DBS
Bruun [38], 1996	Risperidone as a treatment	38	pharmacotherapy
Budman [35], 2001	An open-label study of	10	pharmacotherapy
Gilbert [25], 2014	A D1 receptor antagonist,	18	pharmacotherapy
Jankovic [57], 2010	A randomised, double-blind, placebo-controlled	44	pharmacotherapy
Scahill [58], 1997	Fluoxetine has no marked	7	pharmacotherapy
Stamenkovic [59], 2000	Effective open-label treatment of	14	pharmacotherapy
Wilhelm [29], 2003	Habit reversal versus supportive	32	psychotherapy
Wilhelm [30], 2012	Randomized trial of behavior	122	psychotherapy

A total of 28 articles were used in our study: 20 on DBS, 6 on pharmacotherapy, and 2 on psychotherapy. This encompassed 453 patients, i.e., 154 with psychotherapy, 131 with pharmacotherapy, and 168 with DBS.

^a Only 6/8 reported cases in Motlagh et al. [49] and 3/4 in Servello et al. [55] were used in DBS anatomical target analysis; the 3 excluded cases involved simultaneous DBS to different anatomical targets.

clinical studies were abstracted and analyzed, yielding a patient pool of 168 for DBS, 131 for medication, and 154 for psychotherapy (Table 1). DBS targets included in the studies were the globus pallidus (in 94 patients), thalamus (in 70 patients), and ventral capsule/ventral striatum (in 1 patient; Fig. 1). There was no difference in effectiveness of DBS between targets ($p = 0.792$). There was also no detected difference in effectiveness between anteromedial pallidal DBS targeting and other pallidal (e.g., posterior or more ventral) DBS targeting ($p = 0.4214$).

The 3 treatment groups were similar in terms of mean age and symptoms duration (Table 2). DBS resulted in a significantly larger reduction in YGTSS total score than pharmacotherapy ($p = 0.001$) or psychotherapy ($p < 0.001$; Table 3). Because baseline YGTSS total score was

significantly greater for DBS patients than for those in medication or behavioral trials ($p < 0.001$), and DBS patients had a longer follow-up time ($p = 0.004$ vs. patients in medication trials; $p = 0.173$ vs. patients in behavioral trials), an ANCOVA test was performed to control for baseline YGTSS scores and follow-up length; significance of the effect of DBS was preserved ($p < 0.001$). DBS also had an adverse effect rate of 0.15/case (including 0.04 complications requiring surgical intervention, e.g., infection and lead migration/case) versus 1.13/case for medications and 0.60/case for psychotherapy (Table 4).

Percentage improvement in YGTSS over time was not significantly altered in medication ($p = 0.390$) or behavioral ($p = 0.643$) treatment but approached significance with DBS ($p = 0.094$; Fig. 2).

Table 2. Demographics

	DBS	Medication	Behavioral
Age, years	28.6 (9.6)	24.8 (6.5)	30.4 (6.4)
Duration of symptoms, years	20.8 (7.7)	n.r.	20.7 (9.8)
Length of follow-up, months	18.6 (14.7)	1.7 (0.7)	6.1 (2.1)

Values express the mean (SD). There was no significant difference in age among the 3 treatment arms. There was no significant difference in duration of symptoms between the DBS and behavioral treatment arms (and not enough data available for the duration of symptoms in the medication arm). The length of follow-up for DBS was significantly longer than for medication ($p = 0.004$) but not for behavioral treatment ($p = 0.173$). DBS, deep brain stimulation; n.r., not reported.

Table 3. Percent improvement in YGTSS

Treatment	DBS	Medication	Behavioral
Baseline YGTSS	80.0 (9.8)	54.1 (9.8)	48.2 (2.3)
% improvement	49.9 (17.5)	22.5 (15.2)	20.0 (11.3)

Mean (SD) baseline tic severity and tic severity improvement, measured by baseline YGTSS and % YGTSS reduction, respectively. DBS patients had significantly worse baseline tic severity than those in the pharmacotherapy and psychotherapy groups ($p < 0.001$). DBS was significantly better than pharmacotherapy and psychotherapy ($p = 0.001$ and < 0.001 , respectively). There was no significant difference between pharmacotherapy and psychotherapy ($p = 0.692$).

Fig. 1. Coronal view depictions of the brain stimulation target locations included in our analysis.

Discussion

Practical and ethical challenges exist for conducting a blinded DBS trial [20], and hence our analysis is an essential exploratory step in comparing DBS with conservative measures for TS. Our meta-analysis suggests that DBS may be superior to medication and behavioral therapy at reducing TS symptoms for chronic, adult TS patients. Our mean DBS symptomatic improvement was also in agreement with a recent analysis of aggregate data

from the TS registry [21]. DBS may also result in greater improvement over time (Fig. 2). Several pharmacotherapy studies showed that improvement in tic severity either stagnated or declined despite initial improvement [22–26]. Although several studies have shown that HRT is superior to other forms of psychotherapy, including supportive psychotherapy [27–30], HRT loses its effectiveness over time as well [11, 29]. Thus, it is promising that DBS may provide durable and even improved benefit over time.

Table 4. Incidence of treatment-related events reported

	DBS	Medication	Behavioral
<i>Device-related</i>			
Lead infection	5.2 (1.7)	0.0 (0.0)	0.0 (0.0)
Wound infection	0.6 (0.6)	0.0 (0.0)	0.0 (0.0)
Surgical site pain	1.1 (0.8)	0.0 (0.0)	0.0 (0.0)
Misplaced/ migrated electrode	1.1 (0.8)	0.0 (0.0)	0.0 (0.0)
<i>Neurological</i>			
Tics worse	0.6 (0.6)	0.0 (0.0)	6.6 (2.2)
Dyskinesia	0.0 (0.0)	11.9 (3.1)	0.0 (0.0)
Visual ^a	6.3 (1.8)	2.4 (1.5)	0.0 (0.0)
Coordination ^b	3.4 (1.4)	2.9 (1.6)	0.0 (0.0)
Seizures	0.6 (0.6)	0.0 (0.0)	0.0 (0.0)
<i>Neurobehavioral^c</i>			
Autonomic ^d	4.0 (1.5)	68.7 (4.5)	36.9 (4.4)
<i>Pain</i>			
Headache	1.7 (1.0)	10.7 (3.0)	22.1 (3.8)
Somatic pain	0.0 (0.0)	2.8 (1.6)	32.0 (4.2)
Total	26.4 (3.3)	150.1 ^e (34.7)	120.5 ^e (29.5)

Values express the mean (SD). DBS had far fewer total complications (26.4 ± 3.3) than pharmacotherapy (150.1 ± 34.7) or psychotherapy (120.5 ± 29.5).

^a Blurriness, diplopia.

^b Dizziness, vertigo, unsteady gait, dysarthria.

^c Apathy, fatigue, lethargy, psychosis, sleep disorders, anxiety, depression, aggressiveness, phobias.

^d Nausea, vomiting, eating disorder, weight change, sexual dysfunction, gastrointestinal disturbance, postural hypotension, rhinitis.

^e Incidence >100%, indicating that some participants had >1 adverse event.

Although DBS resulted in fewer adverse events, some of these events were of greater magnitude than events after pharmacological or behavioral therapy. Adverse events unique to DBS include device-related complications that often require additional surgery. However, when more surgery was needed, it was effective at alleviating the issue, and patients did not require further intervention during the follow-up period [31–33]. Patients who required removal due to infection still elected to undergo DBS due to its robust benefits, and they were eager for reimplantation [33]. Moreover, transient side effects, including diplopia, flashing, fatigue, dizziness, and limb convulsions, may be eliminated by adjusting stimulation parameters and electrode settings [34]. Similarly, the treatment of neurobehavioral and autonomic events

Fig. 2. Meta-regression of DBS effectiveness over time. The line is the fitted mean, and the gray area is the 95% CI. The percentage improvement in YGTSS over time (measuring effectiveness over time) is not significantly altered in medication ($p = 0.390$) or behavioral ($p = 0.643$) treatment but approaches significance in DBS ($p = 0.094$).

common to behavioral therapy and pharmacotherapy often requires additional therapy. Many antipsychotic medications are associated with weight gain, a common cause for noncompliance and treatment discontinuation [35, 36].

TS is highly associated with neuropsychological comorbidities. Comorbidity rates are dependent on the patient population and range from 60 to 80% for attention deficit-hyperactivity disorder (ADHD), 11–80% for obsessive-compulsive disorder (OCD), and 13–76% for depression [37]. Common medications prescribed for TS can worsen these comorbidities [25, 35, 38]. Notably, 10/11 DBS studies with data on OCD (via the Y-BOCS), 8/8 studies with data on depression (via the BDI), and 5/5 studies with data on anxiety (via the STAI) demonstrated an improvement in comorbid symptoms (an overall 39.7, 49.1, and 29.5% mean improvement in scores for OCD, depression, and anxiety, respectively). Because TS comorbidity symptoms influence both quality of life and therapy continuation, treatment option decisions must factor in effects on TS comorbidities. Our analysis suggests DBS may provide an advantage over other treatments at effectively addressing comorbidities in adults. Additionally, a recent retrospective analysis supported that DBS is effective at significantly reducing both tics and obsessive-compulsive behavior in TS patients, with no significant differences across targets [39].

Our selected patient pool was constructed to represent the chronic TS patient population. We excluded studies

on participants with a mean age of <16 years, and since TS is a childhood-onset psychiatric disorder, this criterion eliminated many studies especially in the medication and behavioral groups. In the behavior group, we included only reports that studied HRT, since this is the most utilized and accepted behavioral therapeutic modality [10, 40], allowing a more accurate reflection of the current TS psychotherapy patient population. All studies of medication for TS were pooled since no single class of medications has been proven most effective. Including only studies that presented YGTSS total score excluded many studies performed before YGTSS became the most commonly utilized tool for tic severity assessment, thus decreasing our sample size and statistical power but likely skewing our pool to better incorporate up-to-date and novel treatment methods.

Our study has a few limitations. We pooled data from all studies with no weighting for rigor of study. Our DBS cohort had more severe cases of TS compared to the pharmacotherapy and psychotherapy groups. This reflects the fact that DBS is not yet a regulatory-approved therapy for TS, so is currently used on an experimental or off-label basis after other options have failed. Nevertheless, DBS resulted in the greatest improvement in YGTSS scores, and so is efficacious in adult treatment-resistant patients for whom pharmacotherapy and psychotherapy were not effective.

It is impressive to note that there was no correlation between baseline YGTSS score and mean symptomatic improvement in our DBS cohort, suggesting that DBS may be equally effective for patients with extremely severe TS as it is for patients with moderately severe TS (ac-

cording to the Spearman and Pearson correlation tests). Moreover, there was a weakly negative correlation between patient age and mean improvement of symptoms, suggesting that DBS may have a weak tendency toward increased effectiveness in younger adult patients. These results suggest that DBS might yield improved quality of life for longer periods of time if initiated earlier in life. Needless to say, a multicenter double-blind, randomized, sham-controlled trial of DBS for adult refractory TS patients is needed to corroborate our findings, and to move toward regulatory approval.

Acknowledgment

We thank Brandon Bentzley, MD, PhD, for his statistical expertise, and Daniel A. N. Barbosa, MD, for his assistance with figure creation and design.

We dedicate this manuscript to coauthor and late neurosurgeon Dr. Sherman Stein, who made significant contributions to the conception of this work, the study design and its analysis.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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