**Reviews**

**Uncommon Applications of Deep Brain Stimulation in Hyperkinetic Movement Disorders**

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**Abstract**

**Background:** In addition to the established indications of tremor and dystonia, deep brain stimulation (DBS) has been utilized less commonly for several hyperkinetic movement disorders, including medication-refractory myoclonus, ballism, chorea, and Gilles de la Tourette (GTS) and tardive syndromes. Given the lack of adequate controlled trials, it is difficult to translate published reports into clinical use. We summarize the literature, draw conclusions regarding efficacy when possible, and highlight concerns and areas for future study.

**Methods:** A Pubmed search was performed for English-language articles between January 1980 and June 2014. Studies were selected if they focused primarily on DBS to treat the conditions of focus.

**Results:** We identified 49 cases of DBS for myoclonus-dystonia, 21 for Huntington’s disease, 15 for chorea-acanthocytosis, 129 for GTS, and 73 for tardive syndromes. Bilateral globus pallidus interna (GPI) DBS was the most frequently utilized procedure for all conditions except GTS, in which medial thalamic DBS was more common. While the majority of cases demonstrate some improvement, there are also reports of no improvement or even worsening of symptoms in each condition. The few studies including functional or quality of life outcomes suggest benefit. A limited number of studies included blinded on/off testing. There have been two double-blind controlled trials performed in GTS and a single prospective double-blind, uncontrolled trial in tardive syndromes. Patient characteristics, surgical target, stimulation parameters, and duration of follow-up varied among studies.

**Discussion:** Despite these extensive limitations, the literature overall supports the efficacy of DBS in these conditions, in particular GTS and tardive syndromes. For other conditions, the preliminary evidence from small studies is promising and encourages further study.

**Keywords:** Deep brain stimulation, myoclonus-dystonia, ballism, Huntington’s disease, chorea-acanthocytosis, Gilles de la Tourette syndrome, tardive dyskinesia

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**Introduction**

Hyperkinetic movement disorders are a heterogeneous group of conditions, the complexity of which makes treatment challenging. Pharmacologic treatment is often inadequate and fraught with side effects. Past success with surgical lesioning procedures led to the study of deep brain stimulation (DBS) as an alternative approach. This review will focus on DBS in hyperkinetic movement disorders, including myoclonus, ballism, chorea, tardive syndromes, and Gilles de la Tourette’s syndrome. The majority of the literature is in the form of case reports, case series, and small, non-blinded, uncontrolled studies. We will review the major themes and lessons among these reports, and focus on studies involving blinded assessments, on/off stimulation testing, and controlled study design when available. Despite several challenges inherent to summarizing this literature, including wide variation in patient selection, outcome measures, duration of follow-up, surgical targets, and stimulation parameters, we endeavor to present the existing literature in a format that is useful for both clinicians and researchers in this field.

**Search strategy and selection criteria**

A Pubmed search was performed for English-language articles between January 1980 and June 2014. Search keywords were deep
brain stimulation and neurostimulation, and myoclonus, ballism, hemiballism, chorea, hemichorea, choreathetosis, neuroacanthocytosis, choreacanthocytosis, tardive, tic, and Tourette. Studies were selected if they focused primarily on DBS to treat these conditions.

**Myoclonus**

Myoclonus involves sudden brief jerks due to muscle contraction or lapse in contraction and has several possible etiologies. DBS has most often been used for the syndrome of myoclonus-dystonia (M-D), an autosomal dominant disorder associated with mutations in the epsilon-sarcoglycan (SGCE) gene. Action myoclonus begins in childhood or adolescence, in association with cervical and limb dystonia. Medical therapies such as anticholinergics and benzodiazepines are often ineffective and poorly tolerated.

**Patient selection and outcomes**

The earliest reported cases of DBS for M-D targeted the ventrointermediate nucleus of the thalamus (Vim) and globus pallidus interna (GPi) based on experience with these targets for tremor and dystonia, respectively. To date, there have been 49 cases reported in 22 publications (Table 1). In the largest case series to date, Gruber and colleagues studied 10 patients, eight of whom were implanted with both bilateral GPi and Vim DBS. The Unified Myoclonus Rating Scale (UMRS) score and Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) disability score improved significantly in all patients by 61–66% and 45–48%, respectively, compared with the pre-surgical baseline. Combination GPi–Vim stimulation resulted in significantly better UMRS scores than Vim stimulation alone; there was no significant difference between GPi–Vim and GPi alone, or between GPi and Vim each alone. Using a similar approach, Oropilla et al. reported that either target improved myoclonus and dystonia assessed with double-blind on/off testing, but that GPi performed better than Vim.

A meta-analysis by Rughani and Lozano reviewed 40 cases in 17 reports. The UMRS improved by at least 50% in 93.5% of cases, and the BFMDRS improved by at least 50% in 72% of cases. The greater improvement in myoclonus than in dystonia was statistically significant (p<0.001). Although myoclonus improved similarly with either surgical target, there was a statistically significant difference for dystonia favoring GPi over Vim (60.2% vs. 33.3% improvement, p=0.03). In addition, a small number of patients experienced unchanged (n=5) or worsened dystonia (n=1). These results suggest that myoclonus improves more consistently and to a greater degree than dystonia. Factors predictive of positive response included younger age and shorter duration of symptoms.

Since publication of this meta-analysis, there have been seven additional reports of GPi DBS for M-D. Four of these cases were SCGE-positive with an excellent response for both myoclonus and dystonia. Three cases of SCGE-negative patients had less robust but still positive outcomes; however, there is insufficient literature comparing SCGE-positive and negative cases to draw conclusions about their relative response to DBS.

**Stimulation parameters and adverse effects**

In Gruber et al., stimulation parameters were inconsistent, with frequency ranging from 130 to 250 Hz at the Vim, and 130–180 Hz at the GPi, and pulse width ranging from 60 to 210 ms at each target. Vim stimulation was associated with more adverse effects, including dysarthria in seven patients and worsened dystonia in five patients. Non-stimulation-related adverse effects included infections (n=2), lead breakage (n=1), and intracerebral hemorrhage (n=1). In the second largest case series (n=5), no adverse events occurred.

**Summary**

In summary, all published reports of DBS for M-D, the vast majority of which utilized bilateral GPi DBS, describe at least some benefit. GPi stimulation may be more advantageous for dystonia, with similar effects on myoclonus and fewer stimulation-related adverse effects than Vim. There have not been any controlled studies to date. Blinded on/off stimulation testing periods have been short in duration, allowing potential residual benefit, and stimulation parameters have not been specifically compared. All of these limitations should be addressed in future studies.

Reports of DBS in secondary myoclonus include two cases of anoxia-related action myoclonus that have improved, one with unilateral GPi DBS and one with bilateral thalamic DBS.

**Ballism**

Ballism is an involuntary large amplitude movement of the proximal limb, classically associated with subthalamic nucleus (STN) lesions, but also arising due to other structural or metabolic insults and often coexisting with hemichorea (hemiballism–hemichorea or HBHC). In one case of HBHC secondary to hyperglycemia, thalamic DBS reduced chorea and ballism. Ballism was exacerbated off stimulation 9 months post-operatively, which argues against spontaneous remission. In one case of hemiballism and hemidystonia secondary to STN hemorrhage, GPi DBS alleviated both dystonia and ballism. In a revealing case of HBHC following craniopharyngioma resection, both Vim and GPi intraoperative test stimulation suppressed ballism. This very limited literature suggests that either thalamic or GPi DBS may improve ballism. Because hemiballism due to a transient insult may improve with time, future reports would be strengthened by blinded on/off testing over longer follow-up periods.

**Chorea**

Chorea consists of involuntary, irregular movements that flow randomly from one body part to another. It is seen in a variety of conditions, including Huntington’s disease (HD), chorea-acanthocytosis (ChAc), cerebral palsy (CP), and secondary and idiopathic senile forms.

**Huntington’s disease**

HD is a neurodegenerative disease primarily characterized by chorea, cognitive decline, and psychiatric features, but also involving...
other movement disorders including dystonia, parkinsonism, and ataxia. Through effects on swallowing, gait, and balance, chorea can be associated with significant morbidity. Twenty-one cases treated with DBS have been reported in 12 studies targeting GPi (Table 2).28–39 A single case targeted globus pallidus externa (GPe), but did not report clinical outcome.40 Quadruple GPi and STN DBS was utilized in a single case.38

Patient selection and outcomes. All patients had confirmed genetic HD, but other patient characteristics varied among the studies (Table 2). Most reports required chorea to be refractory to medications and causing functional impairment. Patients with unstable psychiatric disease and severe cognitive impairment were excluded, though no clear cut-offs on neuropsychologic testing were reported.

All studies described improvement in the Unified Huntington’s Disease Rating Scale (UHDRS) total score (mean 24.4%) and chorea subscore (mean 58.2%). The largest study was a prospective open-label trial by Gonzalez et al.39 In this study, surgical targeting was performed with interventional magnetic resonance imaging without microelectrode recordings. Improvement in the UHDRS chorea subscore was sustained over the follow-up period, though the total UHDRS score was not significantly improved after 6 months, suggesting that other motor features of HD, such as dystonia and parkinsonism, may not respond as well as chorea over time. This study was limited by its open-label design, unblinded clinical examinations, and lack of quality of life or global impression measures. In two studies, DBS improved chorea-related complications, including dysphagia, involuntary vocalizations, and marked weight loss, with profound impact on quality of life.34,39

Table 1. Cases in the Literature of Deep Brain Stimulation for Myoclonus–Dystonia Syndrome

| Surgical Target | N | SGCE+ (n) | Follow-up (months) (mean, range) | % Change in BFMDRS (mean, range) | % Change in UMRS (mean, range) | Reference |
|----------------|---|-----------|-------------------------------|---------------------------------|-------------------------------|-----------|
| Studies with double-blind on/off stimulation testing | | | | | | |
| Unilateral GPi and Vim | 1 | 0 | 24 | nr+ | 59.5 | Oropilla et al.4 |
| Studies with rater-blinded on/off stimulation testing | | | | | | |
| GPi | 4 | 4 | 50.3 (12–108) | 41.8 (−41.7–77.8)b | 67.1 (59–80.4) | Gruber et al.3 |
| Vim | 2 | 2 | 64.5 (1–128) | 75.5 (70–81) | 43.3 (31.6–55) | Gruber et al.3 |
| GPi and Vim | 4 | 3 | 41.5 (15–76) | 21.0 (0–45.8) | 59.5 (40.7–69.8) | Gruber et al.3 |
| Studies with rater-blinded video assessments | | | | | | |
| GPi | 5 | 5 | 15–18 | 85 (70–91) | 83 (73–93) | Azoulay-Zyss et al.6 |
| Other studies | | | | | | |
| GPi | 31c | 11 | 22.5 (1–128) | 71.8 (50–100) | 64.9 (31.3–89) | Vercueil et al.,2 Beukers et al.,7 Cif et al.,8 Contarino et al.,9 Fonckel et al.,10 Jog and Kumar,11 Kuncel et al.,12 Kurtis et al.,13 Magarinos-Ascone et al.,14 Liu et al.,15 Papuc et al.,16 Wang et al.,17 Yianni et al.,18 Ghosh et al.,19 Uruha et al.,20 Siddiropoulos et al.,21 Kim et al.,22 |
| Vim | 2 | 1 | 16.5 (9–24) | nr | 66.5 (53–80) | Trottenberg et al.,1 Jog and Kumar11 |

Abbreviations: BFMDRS, Burke–Fahn–Marsden Dystonia Rating Scale; GPi, Globus Pallidus Interna; nr, Not Reported; SGCE+, Sarcoglycan-Epsilon Mutation-Positive; UMRS, Unified Myoclonus Rating Scale; Vim, Ventrointermediate Nucleus of the Thalamus.

b81% improvement in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).
+Negative value indicates worsening.
+cIn 17 reports.
Table 2. Cases in the Literature of GPi Deep Brain Stimulation for Huntington’s Disease

| N  | Age | Disease Duration (years) | Follow-up (months) | Stimulation Parameters | % Change UHDRS Total (6–12 months post-operatively) | % Change UHDRS Chorea Subscore (6–12 months post-operatively) | Reference |
|----|-----|--------------------------|--------------------|-----------------------|-----------------------------------|---------------------------------|-----------|
| 1  | 43  | 8                        | 8                  | R: C+2—               | 3.5 V/120 ms/40 Hz                | 31.4                            | 44.0      | Moro et al.²⁸ |
|    |     |                          |                    | L: C+2—               | 5 V/90 ms/40 Hz                   |                                 |           |
| 1  | 41  | 13                       | 12                 | Bilateral: R: C+0—    | 2.8 V/120 ms/180 Hz               | 37.5⁻⁴                           | 50⁻⁴      | Hebb et al.²⁹ |
| 1  | 60  | 10                       | 48                 | Bilateral: 1–2+       | 1.9 V/450 ms/130 Hz               | 5.4⁻⁵                           | 21.4⁻⁵    | Biolsi et al.³⁰ |
| 1  | 72  | 17                       | 12                 | Bilateral: C+1—       | 2.0 V/90 ms/40 Hz                 | nr                              | 82.4      | Fasano et al.³¹ |
| 2  | 57  | 10                       | 24                 | R: 0—1+               | 3.6 V/180 ms/160 Hz               | 45.3                            | 62.5      | Kang et al.³² |
|    |     |                          |                    | L: 0+1—               | 3.6 V/180 ms/130 Hz               |                                 |           |
|    | 50  | 5                        | 24                 | R: 1—0+               | 3.6 V/210 ms/130 Hz               | 11.1                            | 50        | Kang et al.³² |
|    |     |                          |                    | L: 1+2—               | 3.6 V/210 ms/130 Hz               |                                 |           |
| 1  | 30  | 9                        | 24                 | Bilateral: C+0—       | 2.0 V/60 ms/130 Hz                | 15.2                            | 75        | Spielberger et al.³³ |
| 1  | 30  | 10                       | 12                 | Bilateral: C+0—       | 3.6 V/60/130                      | 30.2                            | nr        | Garcia-Ruiz et al.³⁴ |
| 1  | 40  | 3                        | 12                 | Bilateral: C+0—       | 1.5 V/90 ms/130 Hz                | 24                              | nr        | Huys et al.³⁵ |
|    |     |                          |                    |                       | 1.5 V/90 ms/130 Hz                |                                 |           |
|    | 31  | 15                       | 48                 | nr                    | 2.0 V/210 ms/80 Hz                | 17.8                            | 100       | Cislaghí et al.³⁶ |
| 2  | 34  | 7                        | 12                 | Bilateral: C+1—       | 2.0–3.2 V/150 ms/60–80 Hz         | 11.8                            | 73.7      | Velez-Lago et al.³⁷ |
| 25 | 6   | 12                       |                    | Many tried            | Many tried                       | 9.8                             | n/a c     | Velez-Lago et al.³⁷ |
| 1  | 41  | 9                        | 48                 | GPi R:C+2—            | 0.5 V/160 Hz                      | 38.2                            | 50        | Gruber et al.³⁸d |
|    |     |                          |                    | L:C+2—                | 1.0 V/160 Hz                      |                                 |           |
|    |     |                          |                    | STN R: 3–2+           | 5.0 V/40 Hz                       |                                 |           |
|    |     |                          |                    | L: 3–2+               | 5.0 V/40 Hz                       |                                 |           |
| 7  | Mean| 49.71 (±2.27)            | 36                 | Monopolar or bipolar  | 1.4–3.6 V/90–450 ms/130 Hz        | Mean 10.91% (p=0.090)            | Mean 58.34% (p=0.018) | Gonzalez et al.³⁹ |
In order to distinguish ongoing benefit of DBS from spontaneous remission of chorea, unblinded on/off stimulation testing was performed in seven studies, at anywhere from 12 months to 4 years. In the majority, chorea was exacerbated within minutes off stimulation.\(^{29,30}\) In the Gonzalez study, the chorea subscore was significantly different between on and off conditions at 18 months and last follow-up.\(^{39}\) However, in other reports, chorea was unchanged with stimulation off, from 1 to 4 years post-operatively.\(^{31,32,36}\)

Despite overall persistent benefit for chorea, bradykinesia, rigidity, and gait impairment may not respond or may even worsen after DBS. It remains unclear to what extent this is due to stimulation-induced side effects, as some cases improve with a decrease or discontinuation of stimulation\(^{37}\) whereas others do not.\(^{29,31}\) Disease progression likely accounts for clinical worsening post-operatively in some cases. Despite persistent improvement of chorea, several cases have demonstrated progressive bradykinesia, speech impairment, gait impairment, and cognitive decline that may limit the global impression of benefit of DBS.\(^{31,33,39}\) Conversely, bradykinesia and rigidity improved in the on stimulation state for up to 2 years of follow-up in one report.\(^{32}\) One report of GPi DBS for the parkinsonism-dominant Westphal variant of HD showed limited benefit.\(^{36}\) There are mixed results in dystonia-dominant cases.\(^{37}\)

**Stimulation parameters and adverse effects.** Various stimulation strategies were employed in an effort to limit extrapyramidal side effects. Low-frequency vs. high-frequency stimulation demonstrated conflicting results for bradykinesia, rigidity, and gait.\(^{28,29,31,32,37,39}\) In the Gonzalez study, reduction in pulse width improved bradykinesia.\(^{39}\) In a single case of quadripolar GPi and STN DBS, both improved chorea equivalently, but STN improved bradykinesia and oculomotor function more than GPi.\(^{38}\) Other adverse effects were infrequent in published cases. In Gonzalez et al., one patient had a hardware complication and one required lead repositioning.

**Neuroacanthocytosis**

The neuroacanthocytosis syndromes are genetic conditions characterized by prominent chorea and neuropsychiatric symptoms, with red blood cell acanthocytosis. ChAc, an autosomal recessive neuroacanthocytosis associated with VSP13A mutations in the chorein gene, classically causes oromandibular chorea with lip and tongue biting, tongue protrusion or feeding dystonia, and paroxysmal head/neck and trunk movements. Though there is a single case report about the ventral oral part of motor thalamus (Vop) DBS,\(^{41}\) the remainder of the reported cases have selected the GPi target.

**Patient selection and outcomes.** All cases of GPi DBS for ChAc reported to date are summarized in a worldwide retrospective cross-sectional study by Miquel and colleagues.\(^{42}\) Fifteen cases were identified, 12 of which had been previously described in the literature. Molecular (chorein western blot) or genetic confirmation of diagnosis was obtained in 13 out of 15 cases. The mean age at surgery was 38.7 (SD 7.3) years, with mean disease duration of 9.6 (SD 7.2) years, and mean follow-up of 29.5 (SD 23) months. The indications for DBS

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**Table 2. Continued**

| Reference | Contact Configuration | Amplitude/Pulse Width/Frequency | % Change UHDRS Total (6–12months post-operatively) | N/Sm 21/129 | 24.4% (SD 13.1) | 59.2% (SD 21.1) | 38.0% (SD 18.6) |
|-----------|----------------------|-------------------------------|---------------------------------------------|-------------|-----------------|-----------------|-----------------|
| Summary   |                      |                               |                                             | N=21        |                 |                 |                 |

**Abbreviations:** GPi, Globus Pallidus Interna; n/a, Not Applicable; nr, Not Reported; SD, Standard Deviation; STN, Subthalamic Nucleus; UHDRS, Unified Huntington's Disease Rating Scale.

\(^{a}\)Approximate, numerical scores not presented.

\(^{b}\)Only 4-year outcomes reported.

\(^{c}\)No chorea at baseline or follow up.

\(^{d}\)Bilateral GPi and STN leads implanted.
included refractory and disabling hyperkinetic movements (chorea, dystonia, trunk spasms, head drops) in 11 cases, and self-mutilating behavior in six cases. All patients with UHDRS motor scores available (13/15) significantly improved compared with baseline in the early post-operative period (1–5 months, mean improvement 54.3%). At the last recorded visit (6 months or longer) mean improvement was somewhat lower at 44.1%, but 8 out of 13 (61.5%) still had a clinically meaningful benefit of at least 20% compared with baseline. UHDRS independence score (IS) and functional capacity score (FCS) were significantly improved at the early visit, but only the FCS score was significantly improved at last follow-up, suggesting that either waning benefit from DBS or development of non-DBS-responsive symptoms over time may limit independent function. Chorea and dystonia were the most improved symptoms, along with trunk spasms and head drops. Injurious orofacial movements improved in all except one patient, and feeding status improved in six out of nine patients for whom this information was available. Both gait and swallowing outcomes varied greatly, improving if secondary to chorea or dystonia, but failing to improve or even worsening if secondary to parkinsonism. Dysarthria was refractory to DBS, and one patient experienced severe worsening of speech related to stimulation. The severity of the baseline UHDRS motor score, but not age or disease duration, was significantly associated with the degree of improvement on the UHDRS motor score.

McLeod syndrome is an X-linked neuroacanthocytosis syndrome. In a single case, GPi DBS improved chorea and dystonia, but hypotonia continued to limit independent ambulation.43

**Stimulation parameters and adverse effects.** As with DBS for HD, ChAc cases demonstrate the complexity of programming when several movement phenomenologies are present. The majority of the ChAc patients (9/15) received high-frequency stimulation (130–185 Hz) throughout the duration of follow-up. Four patients experienced worsening of chorea with high-frequency stimulation43,44 and two patients experienced worsened dystonia.44 In two cases with blinded on/off testing, chorea improved at 40 Hz, but at 130 Hz chorea and dysarthria worsened and drooling developed, and 10 Hz stimulation had no effect.13 One patient had worsened truncal spasms with low-frequency stimulation.45 In two patients severe truncal hypotonia was non-responsive to DBS.43,46 Optimal stimulation settings thus appear to be highly individualized on the basis of both the presence and the relative contribution of various symptoms to global function. One ChAc patient notably developed “Twiddler syndrome” (manual twisting of device components leading to malfunction).42 There are no reports of exacerbation of seizures.

**Secondary and other chorea syndromes**

There are case reports of DBS for secondary chorea. Unilateral GPi DBS improved hemicheora secondary to STN developmental venous anomaly with microhemorrhage.47 A case of hemicheora secondary to thalamic hemorrhage responded to Vim DBS.48 As mentioned previously, BBHBC improved with DBS in two reports.25,27 A case series reported on four patients with GPi DBS for generalized chorea secondary to cerebral palsy. After 2 years of follow-up, two patients had decreased injurious movements and gains in independent function but none had statistically significant improvement by rating scales.49 Similarly, GPi DBS improved caregiver assessment of daily function in a patient with choreoathetosis and myoclonus in the setting of cerebral palsy.50 One patient with cerebral palsy-associated chorea was treated with Vim DBS with patient-reported marked improvement.50 GPi DBS improved choreoathetosis as well as stereotypic and ballistic movements in a single case.51 A single report of DBS for senile idiopathic chorea utilized unilateral GPi and Vop-thalamus leads and found that thalamic stimulation produced steady benefit over 18 months of follow-up.52

**Adverse outcomes in DBS for chorea**

The rate of post-operative complications in these syndromes appears to be within the range of other DBS indications. There is limited information about the impact of DBS on cognitive and psychiatric comorbidities in these conditions.

**Summary**

In summary, DBS may have a role in alleviating refractory chorea due to various etiologies. The majority of the literature is focused on GPi DBS in HD and ChAc, which appears to improve functional disability in select patients. The response of parkinsonism, dystonia, and hypotonia is more variable. These features may worsen either as a result of disease progression or stimulation, limiting the global benefits of DBS and complicating stimulation adjustments. Symptoms that are not responsive to DBS, such as postural instability and cognitive impairment, may emerge with time and cause significant disability even if DBS continues to control chorea. Further research should include controlled studies focused on optimal patient selection, stimulation approaches, and assessment of benefit over long-term follow-up. In addition, in HD, chorea can lessen over time, and this must be distinguished from DBS-related benefits. Blinded on/off testing would help clarify long-term effects. As DBS may be seen as a palliative treatment, functional outcomes, quality of life, and patient and caregiver-rated impressions of benefit will be important measures of success.

**Tics and Gilles de la Tourette’s syndrome**

Gilles de la Tourette syndrome (GTS) is a childhood-onset neuropsychiatric syndrome characterized by multiple motor and vocal tics. Tics are sudden, repetitive, stereotyped muscle contractions (motor tics) or sounds (vocal tics) that can involve self-injurious behavior. Patients often suffer from concurrent obsessive-compulsive disorder (OCD), attention-deficit hyperactivity disorder (ADHD), and mood disorders. Pharmacologic therapies are associated with side effects including sedation, weight gain, and drug-induced movement disorders. Based on the success of surgical lesioning in medial thalamic targets, the first DBS procedure for GTS was performed in 1999.53
| Target                   | N  | Study Type | Follow-up (months) | Age (years [mean, range]) | % Reduction YGTSS (mean, range if reported) | % Reduction YBOCS (mean, range if reported) | Reference                                                                 |
|-------------------------|----|------------|--------------------|---------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------------------------------------|
| **Thalamus**            |    |            |                    |                           |                                             |                                             |                                                                           |
| CM-Pf                   | 5  | RCT        | 3                  | 28.2 (18–34)             | 44 (−11.9–63.3)<sup>a</sup>                | 44.4                                        | Maciunas et al.<sup>59</sup>                                              |
|                         | 5  | CR         | 6–18               | 23.4 (17–35)             | 70.5 (60–81.8)                              | nr                                          | Pullen et al.,<sup>68</sup> Savica et al.,<sup>69</sup> Lee et al.<sup>70</sup> |
| CM-Voi-Spv              | 6  | RCT        | 12                 | 40.3 (35–48)             | 49 (26.1–94.7)                              | 70                                          | Ackermans et al.<sup>60</sup>                                              |
|                         | 4  | CR         | 8–120              | 36 (20–45)               | 66.3 (7–92.6)                               | 65<sup>b</sup>                               | Vandewalle et al.,<sup>53</sup> Visser-Vandewalle et al.,<sup>65</sup> Ackermans et al.,<sup>66</sup> Duits et al.,<sup>67</sup> Ackermans et al.<sup>71</sup> |
| CM-Pf-Voi               | 31<sup>c</sup> | CS | 3–72               | 32 (17–57)               | 47 (5–88)                                   | 17.3 (−27.5–90)<sup>a</sup>                 | Servello et al.<sup>61</sup>                                               |
|                         | 6  | CR         | 12–24              | 26.4 (19–48)             | 50.6 (29.1–66)                             | 33.0 (−53–100)<sup>a</sup>                 | Bajwa et al.,<sup>72</sup> Kaido et al.,<sup>73</sup> Idris et al.,<sup>74</sup> Rzesnitzek et al.<sup>75</sup> |
| VA/VL                   | 8  | CS         | 12                 | 33.3 (19–56)             | 58                                          | 50                                          | Huys et al.<sup>58</sup>                                                  |
| Vo                      | 7  | CS         | 6–24               | 36.6 (24–52)             | 33 (9.5–48.6)                               | 3 (−47.1–23.8)<sup>a</sup>                 | Marceglia et al.<sup>63</sup>                                             |
| CM                      | 5  | CS         | 4–6                | 34.4 (28–39)             | 25                                          | nr                                          | Maling et al.<sup>64</sup>                                               |
| Thalamus<sup>d</sup>    | 4  | CS         | 6–95               | 28.5 (16–44)             | 44.8 (7–85)                                 | 13.8 (−35–100)<sup>a</sup>                 | Motlagh et al.<sup>56</sup>                                              |
| PF-DM-LM                | 1  | CR         | 6                  | 22                         | 35.9                                        | nr                                          | Vernaleken et al.<sup>76</sup>                                           |
| Pallidal and nigral input regions of thalamus | 3  | CR         | 12                 | 23.7 (22–26)              | 62.0 (35.9–82.6)                             | nr                                          | Kuhn et al.<sup>77</sup>                                                  |
| **Globus pallidus interna** | |            |                    |                           |                                             |                                             |                                                                           |
| Am or Pvl GPi           | 5  | CS         | 3–24               | 37.8 (21–60)             | 29 (10.8–62.8)                              | 26                                          | Martinez-Fernandez R et al.<sup>79</sup>                                |
| Pvl GPi                 | 4  | CS         | 5–48               | 33.8 (25–44)             | 40.75 (−6–88)<sup>a</sup>                   | nr                                          | Dehning et al.,<sup>80</sup> Dehning et al.<sup>81</sup>                 |
|                         | 6  | CR         | 6–51               | 27.8 (16–44)             | 48.8 (20–84)                                | 43 (17–69)                                  | Motlagh et al.,<sup>56</sup> Ackermans et al.,<sup>71</sup> Diederich et al.,<sup>82</sup> Gallagher et al.,<sup>83</sup> Shahed et al.<sup>84</sup>, Dueck et al.<sup>89</sup> |
### Table 3. Continued

| Target                          | N  | Study Type | Follow-up (months) | Age (years [mean, range]) | % Reduction YGTSS (mean, range if reported) | % Reduction YBOCS (mean, range if reported) | Reference                          |
|---------------------------------|----|------------|--------------------|----------------------------|---------------------------------------------|---------------------------------------------|-------------------------------------|
| Am GPi                          | 17 | CS         | 4–30               | 29.1 (17–51)               | 54.3 (0–85.2)                              | 61.9 (26.0–100)                            | Cannon et al., Sachdev et al.       |
|                                 | 2  | CR         | 12–24              | 17 (15–19)                 | 58.2 (55.4–61)                            | nr                                          | Huasen et al., Massano et al.       |
| Ventral GPi                     | 2  | CR         | 12                 | 31.5 (22–41)               | 55.8 (53–59)                              | nr                                          | Dong et al.                         |
| GPi                             | 1  | CR         | 6                  | 21                         | 47                                          | nr                                          | Patel and Jimenez-Shahed           |
| **Anterior limb internal capsule or nucleus accumbens** |     |            |                    |                            |                                              |                                              |                                     |
| NA                              | 4  | CR         | 7–36               | 32 (26–38)                 | 61.1 (41–80)                              | 64.2 (52–84.6)                             | Kuhn et al., Sachdev et al., Neuner et al. |
| ALIC/NA                         | 3  | CR         | 10–30              | 35.7 (27–47)               | 25.4 (−17–68.1)                          | 27.2 (0–54.3)                              | Flaherty et al., Burdick et al., Servello et al. |
| **Combination targets**         |     |            |                    |                            |                                              |                                              |                                     |
| CM-Pf and Am GPi                | 4  | CS         | 20–60              | 33 (30–36)                 | 62.3 (43–76)                              | nr                                          | Houeto et al., Welter et al.        |
| CM-Pf and Pvl GPi               | 1  | CR         | 12                 | 45                         | nr                                          | nr                                          | Ackermans et al.                    |
| Am or Pvl GPi and midline thalamus | 2 | CR         | 37–107             | 33.5 (19–48)               | 0, 72                                      | n/a, 72.4                                  | Motlagh et al.                     |
| ALIC then CM-Pf/Vo/VOi          | 3  | CR         | 3–44               | 31.7 (24–40)               | 45.3 (31.6–60)                            | 14.2 (−21.7–34.2)                         | Servello et al., Shields et al.     |
| Pvl GPi then ALIC/NA            | 1  | CR         | nr                 | 42                         | 49.3                                       | 38.2                                       | Servello et al.                    |

**Abbreviations:** ALIC, Anterior Limb of Internal Capsule; Am, Anteromedial; CM, Centromedian; CR, Case Report with < 3 Patients; CS, Case Series with > 3 Patients; DM, Dorsomedial Nucleus; GPi, Globus Pallidus Interna; LM, Lamella Medialis; NA, Nucleus Accumbens; n/a, Not Applicable; nr, Not Reported; Pf, Parafascicular Nucleus; pvl, Posteroventrolateral; RCT, Randomized Controlled Trial; Spv, Spinal Trigeminal Nucleus; VA, Ventral Anterior Thalamic Nucleus; VL, Ventral Lateral Thalamic Nucleus; Vo, Ventral Oral; Voi, Ventral Oral Internal; YBOCS, Yale–Brown Obsessive Compulsive Scale; YGTSS, Yale Global Tic Severity Scale.

*Negative value indicates worsening.
*Reported in single case (Duits et al. 65).
*One case was unilateral, 18 were followed for 60–72 months, ranges for outcomes reflect these 18 patients reported in Porta et al. 63
*Target was 5 mm lateral, 4 mm posterior, 0 mm beneath anterior commissure-posterior commissure (AC-PC).
*Unilateral.
*Single case of simultaneous CM-Pf/Vo and ALIC/NA outcome not included in analysis.
### Table 4. Cases in the Literature of Deep Brain Stimulation for Tardive Dystonia or Dyskinesias (GPi except where noted)

| N  | Follow-up (months) | BFMDRS Score Used | % Change BFMDRS Mean (range) | % Change in AIMS Mean (range) | % Change in ESRS Mean (range) | References |
|----|--------------------|--------------------|-------------------------------|------------------------------|------------------------------|------------|
|    |                    |                    |                               |                              |                              |            |
| 10 | 6                  |                    | 56 (33–78)                    | 61 (44–75)                   |                              | Damier et al. 126 |
| 5  | 24–96              | M/D                | 71 (23–100)/48 (0–94)         | –                            | 77 (0–73)                    | Chang et al. 129 |
| 1  | 5.9                |                    | 90                            | –                            |                              | Pretto et al. 130,b |
| 1  | 5                  | –                  |                               | 63                            | –                            | Schrader et al. 108 |
| 1  | 6                  | T                  | 91                            | 77                            | –                            | Trottenberg et al. 106 |
| 9  | 18–80              | M/D                | 83 (63.6–100)/68 (25–100)     | 79 (33.3–100)                | –                            | Gruber et al. 119 |
| 6  | 3–39               | M/D                | 86 (58–100)/80 (67–100)       | –                            | –                            | Sako et al. 118 |
| 5  | 6                  | M/D                | 87 (75–98)/96 (80–100)        | 78                            | –                            | Trottenberg et al. 112 |
| 5  | 3–84               | M/D                | 47 (0–92)/55 (0–92)           | –                            | –                            | Egidi et al. 115,b |
| 4  | 8–35               | T                  | 59.8 (6–100)                  | –                            | –                            | Starr et al. 113,b |
| 25 | 3–120 (mean 22.4)  | M                  | 49.4 (–2.4–97)                | 60.3 (42–77)                 | –                            | Eltahawy et al. 107, Krause et al. 109, Franzini et al. 110, Halbig et al. 111, Cohen et al. 114, Kosel et al. 116, Magarinos-Ascone et al. 117, Katsakiori et al. 120,121, Capelle et al. 122, Kim et al. 123, Spindler et al. 124, Trinh et al. 125, Boulogne et al. 128, Zhang et al. 132,e |
|    |                    | D                  | 48.7 (0–100)                  |                              |                              |            |
|    |                    | T                  | 69.0 (31–93)                  |                              |                              |            |

**Abbreviations: –, not reported; AIMS, Abnormal Involuntary Movements Scale; BFMDRS, Burke-Fahn–Marsden Dystonia Rating Scale; D, Disability Subscore; ESRS, Extrapyramidal Symptoms Rating Scale; GPi, Globus Pallidus Interna; M, Motor Subscore; T, Total.**

*Approximate, individual scores not presented.
*Reports of tardive dystonia patients within a larger cohort of primary and/or secondary dystonia patients.
*Outcomes available were averaged, as not all cases reported every outcome.
*Total number of patients in 16 reports.
*Surgical target was subthalamic nucleus rather than GPi.
*Reported in only three studies.
There are 129 cases reported in the literature, 115 of which were recently reviewed.54

**Patient selection and outcomes**

Patient selection criteria vary among the reported cases, and though guidelines have been proposed, components of these criteria are debated.55 Proposed criteria state that tics should be “severe;” however, severity may be poorly captured by rating scales, as tics tend to fluctuate, are suppressible, and may be exacerbated by environmental factors. Another proposed criterion is that tics are treatment refractory, defined as unsatisfactory response or unacceptable side effects to three different medications, including a typical and atypical neuroleptic, as well as behavioral therapy.55 Some authors advocate a minimum age of 25 since symptoms typically improve in early adulthood,55 while others suggest DBS in younger patients may be associated with better tic control and functional outcomes.56 Tics that could result in permanent injury may justify DBS at an earlier age.55 A prospective open-label trial found that lower baseline compulsivity and anxiety scores, but not age at surgery, were significantly associated with tic improvement after DBS.58 Future studies should determine patient characteristics predictive of outcomes and standardize patient selection criteria.

A variety of surgical targets have been utilized with at least partial success in GTS. The pathophysiology of GTS is thought to involve aberrant cortico-striato-thalamo-cortical circuitry, and modulation of this circuitry by DBS at several different targets in the pathway appears to have benefits.

**Thalamus.** The most frequently utilized surgical target for GTS is the medial thalamus, including the centromedian (CM), parafascicular (Pf) and ventro-oralis internus (Voi) nuclei. There are 85 individual cases reported with overall clinical success (Table 3).56,58,77 Servello and colleagues61 published the outcomes of 30 bilateral CM-Pf-Voi DBS cases. There was a statistically significant decrease in the Yale Global Tic Severity Scale (YGTSS) from 75.5 to 40.0 at last follow-up. Since isolated improvement in tics may not ultimately yield functional improvement, it is noteworthy that there was a significant improvement in the Yale-Brown Obsessive Compulsive Scale (YBOCS), depression, anxiety, and patient-rated impact of GTS on a daily life visual-analog scale. These improvements were maintained for at least 2 years in the 19 patients who reached this endpoint. Quality of life and global assessment of function also improved in a prospective open-label stimulation, these rating scales improved moderately, by 40% and 44% respectively, and two of five patients had suboptimal clinical response for unclear reasons. In a crossover study by Ackermans et al.,60 six participants were randomized to 3 months on or off stimulation, followed by crossover, then by 6 months of unblinded stimulation. There was significant improvement in YGTSS (37%) on stimulation compared with off stimulation, with vocal tics improving more than motor tics. The degree of improvement was greater with unblinded stimulation (49%). These studies highlight the importance of the placebo effect in this condition. The Ackermans trial reported stimulation-related side effects in all patients, most commonly lack of energy and subjective visual disturbance.

**Globus pallidus interna.** GPi is the second most commonly utilized target in GTS, and approaches have targeted anteromedial or posterovernal GPi in a total of 37 cases (Table 3).56,57,71,78–90 The largest case series (n=11) targeted anteromedial GPi, and reported significant reduction in motor and vocal tics in all except one patient, as well as improvement in obsessive-compulsive symptoms, quality of life, and global function.55 Dehning and colleagues88 reported six patients who underwent posterovernal GPi DBS, four of whom had a dramatic reduction in YGTSS (97%) and significant improvement in quality of life/global function. However, reports of patients who received little to no benefit raise concern and highlight the need for further study of this target.

**Anterior limb of the internal capsule and nucleus accumbens.** The third most commonly utilized target for GTS is the anterior limb of the internal capsule-nucleus accumbens (ALIC-NA), which has been shown to improve OCD,94 and has thus been targeted in GTS patients with severe OCD. In seven published cases, obsessive-compulsive symptoms responded well, but tic response was highly variable (Table 3).92–97 A single case had worsening of tics and no change in OCD.97 Another strategy reported is “rescue” ALIC-NA DBS if thalamic or pallidal DBS successfully controls tics but not obsessive-compulsive symptoms.96,99

There is a single report of GPe DBS with significant improvements in tic severity, anxiety and depression at 2 years.100 STN DBS was performed in a patient with concurrent diagnoses of GTS and Parkinson’s disease with near complete resolution of tics at 1 year.101

**Comparisons between targets.** Comparison of targets between studies is limited by variation in anatomic coordinates utilized, small sample sizes, variable length of follow-up, and heterogeneous patient and clinical characteristics. Both Hourieto et al.,102 and Welter et al.103 attempted to overcome these limitations by comparing targets within individual patients in a blinded fashion (Table 3). In Hourieto et al.,102 CM-Pf thalamus and anteromedial GPi stimulation alone and in combination yielded similar improvement in tic severity (65–70%) and self-injurious behavior, while thalamic stimulation was more beneficial for mood and impulsivity. In Welter et al.,103 GPi stimulation outperformed thalamic or combined stimulation. In both of these
studies, sham stimulation resulted in worsening of tics, reducing the likelihood of placebo effect.

**Adverse outcomes**

While psychiatric symptoms are stable or improved in most cases, there are reports of refractory or worsening psychiatric symptoms after both thalamic and ALIC/NA DBS. In addition, Servello et al. found a significantly increased incidence of post-operative infection of 18% in GTS compared with 3.7% in other disorders. Possible explanations include compulsion toward touching the surgical wound leading to infection, or even altered immune function in GTS.

**Summary**

In summary, both medial thalamic and GPi DBS may be efficacious in GTS. ALIC-NA DBS appears to improve OCD but has not demonstrated consistent efficacy for tics. In light of suboptimal results in some cases, further studies are necessary to elucidate how patient characteristics, surgical procedure, and stimulation parameters impact outcomes. While GPi DBS may seem more successful, an adequately powered study comparing effects on motor and vocal tics, self-injurious behaviors, psychiatric, and functional outcomes, and tolerability is required. Future studies must also control for placebo effect, distinguish the effects of DBS from fluctuation of tics, and include intention-to-treat analyses to avoid excluding non-responders lost to follow up.

Finally, new advances in DBS technology may allow individualized therapy, such as scheduled stimulation personalized to the characteristics of tics, or even responsive to electrophysiologic abnormalities in individual patients.

**Tardive syndromes**

**Patient selection and outcomes**

Tardive syndromes are a heterogeneous group of movement disorders resulting from use of dopamine receptor blocking agents. Tardive dyskinesia (TD) can involve both choreiform and dystonic movements, while tardive dystonia can also occur in isolation. The first report using DBS for TD by Trottenberg et al. reported improvement with posteroventral GPi but not Vim stimulation.

To date, there have been 73 cases of GPi DBS for TD (including tardive dystonia) reported in 26 studies (Table 4). All except two recent cases have been reviewed previously. Overall, these reports support that GPi DBS improves refractory TD. The mean improvements in BFMDRS motor and disability subscores were 71% and 65% in Spindler et al., and 80.9% and 74% in Mentzel et al. A single prospective trial demonstrated statistically significant improvement with double-blind on/off testing. Among the studies, dyskinesia and dystonia responded similarly, with no consistent relationship between anatomic distribution of movements and response. Phasic dystonic movements responded better than fixed postures. Mentzel et al. did not find any covariates that significantly correlated with response. There are also reports of unsatisfactory response for unclear reasons. Responders maintained benefits over the duration of follow-up, which was at least 2 years in more than 20 patients, and was as long as 10 years in one patient. The clinical heterogeneity of these syndromes, often involving mixed movement disorders of dystonia and choreoathetosis, complicates measurement of motor outcomes. Compared with other etiologies of secondary dystonia, Saleh et al. found that TD had a better response, with BFMDRS improvement of 73% for TD (n=33) and 35% for other etiologies (n=84).

There is a single report of STN DBS for TD, with excellent responses in two patients.

**Stimulation parameters**

Stimulation parameters vary widely among the reports, possibly due to variability in precise lead locations and/or heterogeneous clinical manifestations. Frequency ranges from 40 to 185 Hz, with most studies using 130–160 Hz. Nine studies use higher pulse widths (>200 ms) as have classically been utilized in primary dystonia, while nine studies used lower pulse widths ranging from 60 to 90 ms. One possible stimulation-related side effect of GPi DBS is extrapyramidal gait disorder with parkinsonism or freezing of gait. Schrader et al. reported that over their entire dystonia population treated with DBS, 8.5% developed a new gait disorder that was likely related to stimulation, including two patients with TD.

**Adverse outcomes**

The surgical complication rate was similar to that in other GPi DBS indications. While not all studies followed psychiatric rating scales post-operatively, overall there appear to be very few cases of worsening or new psychiatric comorbidities. There was a significant improvement in mood in some reports. There is a single report of worsened depression in three of 10 patients and a single report of psychosis relapse.

**Other uses of DBS in hyperkinetic movement disorders**

**Paroxysmal non-kinesigenic dyskinesial/dystonia**

Paroxysmal non-kinesigenic dyskinesia/dystonia (PNKD) is characterized by episodes of choreiform, dystonic, or ballistic movements. It may be genetic due to MR1 mutations, or may be secondary. Three reported cases improved with DBS; none had MR1 mutations and two were associated with peripheral injury. Two cases utilized GPi DBS, and one utilized Vim DBS followed by additional GPi DBS.

**Lesch–Nyhan disease**

Lesch–Nyhan disease is an X-linked recessive neurobehavioral disorder, characterized by dystonia and self-injurious behavior. A single case report of anteromedial and posteroventral GPi DBS demonstrated that posteroventral GPi stimulation improved hyperkinetic movements. In both this case and a prior report, GPi DBS improved self-injurious behavior.
Other secondary dystonia

DBS has been utilized for secondary dystonia due to a variety of etiologies, including neurodegeneration with brain iron accumulation (NBIA), X-linked parkinsonism-dystonia (Lubag syndrome), vascular, encephalitic, hypoxic-ischemic, and post-traumatic etiologies. It is beyond the scope of this review to discuss specific indications, and these have been recently reviewed. Over 100 cases of DBS for secondary dystonia have been reported, the majority targeting GPi. Outcomes are variable, but broadly fall within the 20–40% improvement range on BFMDRS. In general, outcomes appear to be poorer in the presence of tonic dystonia, pyramidal deficits, or structural lesions or atrophy in the basal ganglia.

One specific secondary dystonia that has been a notable focus of DBS research is cerebral palsy. There have been two prospective open label studies demonstrating significant improvement on motor and disability scores. Variability of outcomes, with some patients receiving minimal or no improvement, may be related to clinical heterogeneity. In addition, lead location appeared to be variable in cerebral palsy compared with other disorders, potentially related to structural abnormalities.

Placebo effect in DBS studies

The placebo effect complicates the assessment of DBS efficacy in the conditions discussed. There are frequently neuropsychiatric features, and motor symptoms may vary depending on psychological factors. In Parkinson’s disease, the placebo effect may account for up to 39% of the benefit of active DBS in crossover trials. The magnitude of the placebo effect in hyperkinetic movement disorders is unknown. In studies that included a double-blind clinical assessment or randomized crossover design, stimulation was activated prior to the blinded study period, resulting in possible unblinding of the patients and/or clinicians. Despite these limitations, patients improved consistently and significantly on stimulation compared with blinded off stimulation. This is highly suggestive of efficacy beyond a placebo effect. However, open-label extension periods resulted in further improvement. It is not clear if this is entirely related to unblinding or due to increased benefit with greater duration of stimulation. The sample size was too small to analyze differences between patients randomized to active vs. inactive stimulation first, but this would help elucidate the role of expectation in those patients receiving inactive stimulation first. Future studies should strive to determine the role of placebo effect in DBS for these relatively rare indications.

Conclusion

Uncommon uses of DBS in hyperkinetic movement disorders for which the current body of literature supports efficacy include M-D, HD, ChAc, GTS and TD. The most common surgical target is GPi, except for GTS in which thalamic targets are most commonly utilized. DBS is a promising therapy for these debilitating conditions; however, there are several limitations and concerns. For instance, there is a need for standardized patient selection criteria and determination of characteristics predictive of outcomes in these very heterogeneous conditions. Double blind, controlled studies with sufficient duration of follow-up are necessary to discriminate the effects of DBS from the placebo effect and natural disease course. There is a great need for comparison between surgical targets in larger prospective controlled studies, which may also provide guidance regarding the appropriate target selection for specific patient characteristics. Greater attention should be paid to functional outcomes. There are also common challenges in selecting stimulation parameters, with potential worsening of certain components of these multifaceted movement disorders. In summary, while further studies are necessary, DBS appears to be a beneficial therapeutic option for several hyperkinetic movement disorders, and provides an encouraging basis for future study.

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