**Abstract:**

When considering Deep Brain Stimulation (DBS) surgical treatment of dystonia syndromes, it is important to consider multiple aspects of the disease and its presentation. It is crucial to know if the dystonia is idiopathic, inherited or acquired as well as focal, segmental or generalised. Careful phenotyping of idiopathic as well as inherited dystonias and accurate diagnosis of acquired dystonias informs the decision-making process for patients and clinicians by providing them with useful predictors of outcomes of the proposed surgery. Here, we provided a review of the current literature, highlighted the areas where evidence is scarce and suggested future directions for research.

1. **INTRODUCTION**

Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal (often repetitive) movements, postures or both. Dystonic movements are typically patterned, twisting and may be tremulous.[1, 2]. Dystonia syndromes are currently classified along two main axes: clinical features and aetiology [3]. In the current classification five descriptors are utilized to specify clinical features: age at onset, body distribution, temporal pattern, coexistence of other movement disordersand other neurological manifestations [3]. The aetiology is an evolving area due to the constant discover of new causes of dystonia. The etiologic classification includes inherited (dystonia forms of proven genetic origin) and acquired (dystonia due to a known specific cause) dystonias as well as idiopathic (genetically unclassified; sporadic or familial) dystonias [3].

The term “primary” was previously used as an etiological descriptor for genetic or idiopathic cases in which dystonia is isolated and there is no consistent pathologic change [2]. However, the latest classification of Albanese et al. [3] suggested to consider the two components of the etiological axis separately.

On the other hand, the term “secondary” dystonia was used as antithetical to primary and indicated non-isolated dystonia, a defined pathology or more generally a known aetiology [2].

[2].

The abnormal postures are the visible motor dysfunction of dystoniabut there is a significant body of evidence suggesting that failures in sensorimotor integration and pure sensory abnormalities are also of relevance in the pathophysiology of dystonia [4].

There remain gaps in knowledge concerning the treatment of various phenotypes of dystonia, especially phenotypes termed “complex dystonia”. Consequentially, there is no consensus regarding the types of appropriate treatments as well as the correct timing for each therapyand especially so for invasive procedures as Deep Bran Stimulation (DBS) of the basal ganglia.

The pathophysiology of dystonia is not known precisely, it follows that current management is empirical.

Since the first published case in 1977 [5], DBS has been increasingly used as the treatment for dystonia syndromes, especially in patients in whom dystonia is sufficiently severe; where dystonia is refractory or not responding to drugs and/or botulinum toxin injections and the chance of success by DBS is agreed by the patient to justify risks, complications and morbidity of surgery.

There is clear evidence that DBS modulates cortical excitability; the stimulation interrupts pathological somatosensory activities and is associated with changes in cortical neurones – both numbers and connections – which is the neuroplasticity phenomenon [6-8]. Although the initial DBS anatomical target in dystonia was the thalamic ventralis intermedius nucleus (Vim), this is now almost completely replaced by the globus pallidus internus (GPi) – due to outcome analysis (Figure 1).

**Figure 1: Proton density image demarcating Gpi**



Another promising DBS-target for dystonia is the subthalamic nucleus (STN) [9-15], although some studies have still targeted the thalamus [16-20] or the cerebellum [21, 22]. It is possible that different subtypes of dystonia have a better response to stimulation of different targets, implying a different pathophysiology.

Although some dystonic movements (phasic dystonia) improve shortly after activation of DBS, a sustained improvement usually develops weeks or even months after the stimulation is turned on [23, 24]. The pathophysiological basis for this delay in response is not understood, though plausibly is related to such as neuronal plasticity or rebalancing of networks. The clinical outcome of phasic-type cervical dystonia has been shown to be better than that of tonic-type cervical dystonia following the DBS of GPi [19]. Cury et al provided evidence suggesting a dramatic efficacy of DBS in younger patients with shorter disease duration [25]. Overall, DBS produces positive changes in clinical status as well as quality of life in dystonia patients. However, an overall non-responder rate of approximately 25% has been reported [26].

This review aims to highlight specificities of the use of DBS in different dystonic syndromes to tailor treatment, predict outcomes and meet social and quality of life needs. We believe that enhancing knowledge in this field is essential to build a consensus regarding the most appropriate and successful therapy, the appropriate timing and, consequentially, to be able to pre-operatively inform individual patients of their options based on management guidelines. This information will also allow planning of future research priorities and influence public health policies for the group of dystonic patients.

However, it should be remembered that even for “ideal” candidates the response rate is not 100%; nor by contrast for “poor” candidates is the response rate zero – hence individual judgements have to be made against the natural history of the condition and non-surgical management strategies.

1. **OUTCOMES OF DBS IN PRIMARY DYSTONIAS**

The responder rate to DBS in dystonia patients depends to the type as well as the aetiology of the dystonia syndrome.

Interestingly, a meta-regression involving 344 patients with different types of dystonia (10 patients with myoclonus dystonia, 19 patients with heredodegenerative dystonias and 93 patients affected by an acquired dystonia) found a mean improvement of 60.7 % on the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor subscore [27]. In line with these results, Vidailhet et al. highlighted an improvement of 51 % at 1 year and 58 % at 3 years in patients with isolated generalized dystonia [28].

A German multicentre, sham‐controlled, randomized study on 40 patients with isolated segmental or generalized dystonia treated with bilateral GPi–DBS [26] showed a greater reduction of dystonic symptoms in the treatment group (P < 0.001). After switching all patients into “stimulation ON”, a mean reduction of dystonic symptoms of 48% was obtained at 6 months follow–up. The subgroup of generalized dystonia showed a continuous improvement at 3 and 5 years follow–up [26].

A recent meta-analysis conducted on 24 studies and involving a total of 523 patients with isolated segmental or generalized dystonia showed that DBS leads to a significant improvement of 65,2% on BFMDRS at 6 months post-surgery and continuously at the next follow-up visits (mean follow-up: 32.5 months, range: 6–72 months) [29]. Even patients with severe dystonia and long duration of disease showed significant improvement with DBS, although other studies reported a significant association between DBS outcome and shorter disease duration as well as lower severity score at the time point of the surgery [26, 30-32].

A recent retrospective study on 14 idiopathic dystonia patients treated with STN-DBS showed a continuous motor improvement of 59.0% at 1 month, 85.0% at 1 year and 90.8% at 5 years after the operation on BFMDRS. Moreover, a continuous improvement of the quality of life was reported. There were no substantial side effects [9]. Other published papers showed similar data on clinical effect of DBS in dystonia [25, 33-35].

The most common type of idiopathic focal dystonia is the cervical dystonia, which is frequently refractory to medications. The efficacy of DBS in pharmaco-resistant cervical dystonia is confirmed by several studies. A case series of 3 patients with idiopathic cervical dystonia [36] and another series of 2 patients [37] demonstrated a relevant long-term reduction of dystonic postures with GPi‐DBS. The latter series highlighted more than 70% improvement on BFMDRS [37]. A more recent trial of 32 medication-refractory patients randomly assigned to Gpi-DBS and 30 medication-refractory patients randomly assigned to sham stimulation confirmed a significant benefit of DBS on cervical dystonia. Indeed, after 3 months of neurostimulation the reduction in dystonia severity was significantly greater with neurostimulation compared to sham stimulation with an improvement of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) by 26% and 41% in the DBS group compared to 6% and 11% in the sham-stimulation group [38]. However, 21 adverse events (5 serious) occurred in 11 (34%) patients in the neurostimulation group versus 20 (11 serious) in nine (30%) patients in the sham-stimulation group. Serious adverse events were related to the implant procedure or the implanted device. The most common non-serious side-effects were dysarthria, dyskinesia, worsening of dystonia and depression [38].

Other four studies identified by Rodriegues et al. [39] confirmed the long-term benefit of GPi-DBS in cervical dystonia with a mean improvement from 47.6% to 70% as well as improvement in the quality of life (follow-up of 2.5-10 years). Two patients with unsatisfactory response to GPi-DBS had an improvement after the subsequent selective periphery denervation [23]. However, a meta-analysis on DBS versus peripheral denervation for cervical dystonia showed no significant difference in the magnitude of reduction of TWSTRS score [40].

Gpi-DBS has produced significant improvement in patients with refractory craniocervical dystonia, including Meige‘s syndrome. A long-term follow-up study of 12 patients showed an improvement of BFMDRS motor part by 53% after 6.5 years from the surgery (47% for eyes symptoms, 56% for mouth involvement and 64% for speech/swallowing difficulties) [41]. Wrang et al. performed a meta-analysis on 69 cases with craniocervical dystonia treated with GPi-DBS and 6 patients with STN-DBS demonstrating similar outcomes between the two targets with a mean improvement of 56% on BFMDRS even in patients with severe preoperative symptoms (mean follow-up was 28 months after the surgery) [42].

Medically intractable blepharospasm cases associated with the cranio-cervical dystonia showed dramatic reduction of symptoms severity when treated with bilateral GPi-DBS [43-45]. On the contrary, some authors showed variable and inconsistent responses to GPi-DBS in patients with isolated blepharospasm and in Meige’s syndrome [31, 46-48]. Overall, the clinical success of DBS in patients with orofacial dystonia is generally inferior compared to cervical dystonia patients [41].

DBS has been particularly useful in complex dystonia cases. Dulski et al presented a case of deafness-dystonia syndrome presenting with segmental cranio-cervical dystonia, jaw-opening, tongue protrusion, retrocollis and gradual overflow including upper limb dystonia with a positive outcome after Gpi-DBS [49]. In line with these results, two other cases of deafness-dystonia syndrome of unknown cause were reported showing significant positive outcome after Gpi-DBS [50, 51].

Unilateral thalamic DBS performed for essential tremor showed incidentally a benefit on the coexistent spasmodic dysphonia documented by a significant improvement on the Unified Spasmodic Dysphonia Rating Scale [52].

Primary limb dystonia is underrepresented in the current scientific literature. There have been described some positive results of writer‘s cramp cases treated with thalamic DBS [19, 53]. GPi-DBS produced successful clinical improvement in the dominant hand in a cohort of children with primary dystonia/dystonia-plus syndrome [54]. Gpi-DBS is an effective treatment also in patients with focal limb dystonic tremor without associated generalized dystonia, which is the type of tremor well-known to be refractory to pharmacological treatments [55, 56]. A task-specific pharmacologically resistant focal dystonia of the head along with intermittent left arm cramp during golf playing improved substantially under GPi-DBS [57].

Patients with generalized dystonia respond well to DBS. A blind study of 22 generalized idiopathic or inherited dystonia patients receiving GPi-DBS have shown a BFMDRS-improvement of 54,6% at 12 months follow up after surgery compared to sham-stimulation [58]. Another study proved a reduction of generalized dystonia by 42%–61% on BFMDRS at 5 years follow up after DBS [59].

Inherited generalised dystonias are commonly associated and potentially caused by the mutation of particular genes and represent the so-called “monogenic dystonias”, which are designated with a “DYT” prefix followed by the gene number (from DYT1 to DYT29) However, monogenic dystonias can also have a segmental or polifocal presentation. Many monogenic dystonias are isolated dystonias, although some of them (e.g. DYT 11) fit into the complex dystonia category [34]. GPi-DBS has been proven effective in treating refractory or poorly responsive to medication monogenic dystonic syndromes with particular research focus on DYT-1 and DYT-6 [34, 48, 50].

DYT1 was the first monogenic dystonia discovered and it is characterized by higher prevalence in people of Ashkenazi Jewish descent [60]. It presents in childhood or adolescence involving at the onset a single limb with a spread within 1–3 years to all four limbs [60]. DYT1 is an autosomal dominant disease with low penetrance caused by a mutation in the torsin 1a (TOR1a) gene [61].

Of all dystonias treated with neurostimulation, DYT1 has shown the best response in several studies [48, 59]. It has been reported up to 60% improvement on BFMDRS in 90% described patients in the first year after GPi-DBS, which persisted (although with 40% decrease on average on the same rating scale) in the subsequent years [34, 50, 59, 62, 63]. Suggested predictors for a good clinical outcome of GPi-DBS include absence of fixed skeletal deformities, younger age at surgery and short disease duration [27, 32].

A disease stabilisation of DYT1 dystonia during a long-term follow-up of 15 years has been reported in one patient treated with GPi-DBS appearing to modify the natural disease progression and provide excellent long-term symptom control [64].

The autosomal dominant DYT6 dystonia is caused by mutations in THAP1 (THAP domain-containing apoptosis-associated protein 1) gene. DYT6 manifests itself with cervical dystonia in 25% of cases but phenotypically can also begin with dystonic posture of an arm or subsequently generalize similarly to DYT1 [65]. Moreover, DYT6 frequently presents with a laryngeal and/or oromandibular dystonia, which are phenotypes usually less responsive to DBS [50]. Generally, the response to neurostimulation in patients with DYT6 is less robust than in those with DYT1, with only 30% improvement on BFMDRS in 60% of patients in the first year following DBS [59]. However, subsequent improvement in the following years has been documented [50, 59, 66].

This difference between DYT1 and DYT6 is thought to be due to differences in the affected anatomical circuits [67, 68].

Some reports have suggested that GPi might be not the ideal target for the patients with THAP1 mutations [59, 69, 70].

DYT5 (the so-called dopamine-responsive dystonia) typically has an excellent response to very low doses of dopaminergic agents and therefore requires no other therapy [71].

DYT12 (the rapid-onset dystonia-parkinsonism) is characterised by an onset over hours and days of a severe generalized parkinsonism as well as of a predominantly bulbar and trunk dystonia with a rostro-caudal gradient. It can occur at any age, although the typical onset is in late adolescence to early adulthood [72]. DYT12 is known to be refractory to dopaminergic medications and to GPi-DBS with isolated case-reports describing poor response [50, 73].

Some case-reports have presented positive outcomes of DBS in patients with generalized dystonia due to the autosomal dominant anoctamin-3-mutation (ANO3 mutation; DYT24) [74-76], PRKRA-mutation (DYT16) [77] and GNAL (DYT25) [62, 78, 79]. However, ANO3 mutations have been linked with tremor-dominant cervical dystonia and it has been commonly experienced that dystonic tremor responds better to Vim-DBS than GPi-DBS [50]. Interestingly, five patients with GNAL mutation (DYT25) showed higher early response rates to DBS than DYT6 patients (p = 0.047). The decrease in dystonia motor scale score in the GNAL group was 46.9% at early follow-up and 63.4% at late follow-up [78].

DYT28 is an early onset generalized dystonia with an early involvement of the low extremities and successive cranial progress [80, 81]. Ten patients with DYT28 who underwent DBS surgery presented a dramatic clinical improvement with the ability to walk independently. Interestingly, the improvement was greater in the youngest patients [34, 81]. Three other patients with DYT28 were also reported to have a partial response to GPi-DBS [82].

Among the inherited combined dystonias, consistently positive responses to GPi DBS have been reported for the X-linked dystonia-parkinsonism (Lubag) and the myoclonus-dystonia syndrome.

The X-linked dystonia-parkinsonism or DYT3 has a typical onset in the later adulthood and it has showed a satisfactory improvement with DBS in several case series [34, 83-85]. A report of three patients with X-linked dystonia parkinsonism showed a sustained improvement of 63.5% in motor sub-scores of BFMDRS after the pallidal DBS (mean follow-up was 45.7 months) [86].

The myoclonus-dystonia (DYT11) has a phenotype characterised by dystonia with action induced myoclonus. The dystonia typically involving the neck and the upper body in 20% of the cases. Cases refractory to medical treatments have been shown a good response to GPI-DBS with a more than 70% improvement on the BFMDRS after the implantation [34, 50, 87, 88]. A long-term retrospective study on nine patients with DYT11 (6 treated with both bilateral GPi and Vim-DBS, 2 with bilateral GPi-DBS and 1 with bilateral Vim-DBS) also concluded towards the favourable outcomes after a mean follow-up of 5 years after the procedure. The myoclonus score decreased by 65.5% and the dystonia score by 48.2% at the last follow-up. Both DBS targets were equally effective and safe [89]. Some reports suggested that the dystonic tremor of DYT11 patients may respond better to thalamic DBS than to GPi-DBS [89-91]. However, a recent study showed a similar outcomes in myoclonus-dystonia patients treated with Vim-DBS and those with GPi-DBS [19]. A meta-analysis of 34 studies reported that 91.8% patients had a significant mean improvement on the BFMDRS motor scores at different time intervals (e.g. 71.1% at more than 36 months). 79.6% patients showed an improvement more than 50% on BFMDRS-M scores [92]. At the same time, the myoclonus reduction was more significant than dystonia improvement [64, 87].

A combined targeting of VIM and GPi in a prospective study of eight patients with DYT11 [90] showed approximately 50% improvement of dystonia and 60% improvement of myoclonus at a mean follow–up of 62 months (range, 1–108 months). Both VIM–DBS and GPi–DBS reduced the symptoms similarly according to BFMDRS and other scales. A higher prevalence of side effects caused by VIM‐DBS (dysarthria and worsening of dystonia) was reported [90].

Two cases of combined DYT1 and DYT11 mutations treated with DBS were described. One patient improved significantly with VIM-DBS, the other one underwent a subsequent GPi-DBS with a significant positive response [93].

1. **OUTCOMES OF THE DBS IN SECONDARY DYSTONIAS**

Tardive dystonia (TD) is a significant side effect of long term treatment with antidopaminergic drugs, which often causes an important disability and is resistant to medications [94]. TD typically manifests as an isolated segmental or generalized dystonia, prominently affecting the trunk [95]. It could be also combined with other tardive motor symptoms (tardive dyskinesia). The prognosis in terms of remission or even reduction in symptoms remains poor even after stopping the triggering drug [24].

GPi‐DBS has been used as a treatment option in some patients with TD. A report of 5 patients [28] described a complete remission of symptoms in four of them within the first week after surgery. Of note, there was a persistent efficacy after 6 months and over the long‐term (range: 18–80 months; mean ± standard deviation: 41 ± 21 months) in the initial group and in another four patients (mean BFMDRS improvement of 71%) [96]. A controlled trial of 10 patients with TD undergoing GPi-DBS showed a 61% improvement on the Extrapyramidal Symptoms Rating Scale (range: 44%–75%) and 56% on the Abnormal Involuntary Movement Scale (range: 33%–69%) at 6 months follow–up [97]. Other studies reported an 80% improvement on BFMRS score [98-100]. Shaikh et al. showed a rapid improvement in four out of eight TD patients treated with GPi-DBS, while the other four patient presented a rapid response of neck and trunk dystonia followed by gradual resolution of residual symptoms over 48 months [100].

A recent controlled blinded randomized trial of 25 patients with tardive dystonia/dyskinesia (12 active and 13 sham neurostimulation) resulted in a significant and pronounced improvements by 41.5% in those treated with GPi-DBS [101]. The BFMDRS score improved by 22,8% within the neurostimulation and non-significantly within the sham group (12%) compared to the baseline severity of dystonia three months post-randomisation [101].

A long-term (65.6 ± 30.4 months, range: 12-105 months) follow-up of bilateral STN-DBS for refractory TD in 10 patients showed a significant and persistent improvement [102]. At the first follow-up, BFMDRS motor and disability scores had improved by 55.9% (± 28.3%) and 62.6% (± 32.0%), respectively. At the second follow-up, BFMDRS motor and disability scores improved further by 87.3% (±17.0%) and 84.3% (± 22.9%), respectively. This benefit was sustained at last follow up [102].

Overall, a systematic review and meta-analysis of 35 studies with 117 patients undergone DBS (mainly GPi-DBS) for TD concluded to a mean improvement of 62 % (± 15%) on the Abnormal Involuntary Movement Scale (reported in 51 patients) and of 76% ( ± 21%) on the BFMDRS (reported in 67 cases) [103]. Reported adverse events were surgery-related in 7 patients, stimulation-induced in 12 and psychiatric in 3 patients [103].

Dystonias caused by hypoxia, traumatic brain injury, neurodegenerative disorders (e.g., neurodegeneration with brain iron accumulation [NBIA], Wilson's disease) represent other acquired dystonias. Data on DBS in this group of dystonic syndromes are scarce and based on case reports or small studies [24, 104].

Perinatal hypoxia manifesting as cerebral palsy (CP) is one of the common aetiologies of dystonia, being frequently resistant to the pharmacological treatment. A prospective study of 13 CP adults patients treated with GPi-DBS showed a motor function improvement by 24% (BFMDRS) after 12 months of GPi‐DBS compared with baseline [105]. Nevertheless, individual BFMDRS showed a large variation from −7.5% (worsening) to +55% (improvement) [105].

A meta-analysis on DBS in 68 CP patients proved only a modest effect of GPi-DBS (motor and disability BFMDRS improved by 23.6% and 9.2% after 12 months, respectively) [55]. However, a long-term recent study on 15 CP patients showed a 49% motor improvement after a mean follow-up of 4.4 years [105].

The different outcomes might reflect the heterogeneity of the population [105].

Bilateral GPi-DBS was reported to be effective in reduction of motor symptoms in CP patients, although the improvement ranged from a mean reduction of 1.2% to 49.5% on BFMDRS [106]. The responsiveness of dystonia to GPi-DBS in CP is less beneficial than in patients with idiopathic or genetic dystonias showing substantial improvement of motor symptoms and disability with pallidal stimulation [37, 107, 108].

Five patients with disabling post-traumatic dystonia treated with DBS (2 patients with GPi-DBS, 2 patients with STN-DBS and one patient with Vim-DBS) showed an improvement in BFMDRS scores from 52.4% to 78.6% [109].

The post-stroke dystonia is classically caused by lesions along the cortico-striato-pallido-thalamo-cortical or cerebello-thalamocortical pathways. It often presents months or years after stroke. A literature review on post-stroke DBS [110] found 16 cases on a total of 26 patients with poststroke dystonia, who underwent DBS (mainly GPi-DBS). Outcome varied widely. Some centres reported marked and sustained improvement and others only minor or transient benefit. Differences in size and location of brain injury, anatomy and electrode localization may explain this variability. One case (not included in the aforementioned review) of ventral anterior internal capsule - ventral striatum-DBS in a patient with right posterior cerebral artery stroke with a left-sided dystonia described a marked improvement after surgery in terms of dystonia and allodynia [111].

Dystonic camptocormia rarely occurs as an isolated focal idiopathic dystonia. A retrospective study of 3 patients presented a complete improvement of symptoms with GPi‐DBS at 38, 39 and 45 months follow-up. No relevant side effects were reported [112]. A case-report of idiopathic camptocormia described a 50% improvement of trunk dystonia and 90% improvement of cervical dystonia on BFMDRS after DBS [113]. However, camptocormia and Pisa-syndrome occur more frequently secondary to the Parkinson’s disease (PD), extensor myopathies, anterior horn cell disorders and muscle disorders. DBS has been tried with variable success in severe PD cases with dystonic camptocormia and Pisa-syndrome.

A patient with PD and Pisa-syndrome was treated with STN-stimulation after being resistant to other treatment options, including botulinum toxin injections. During left STN–DBS programming the right-sided lateral deviation worsened with voltage increment and improved with voltage reduction [114]. Another case-report presented a successful bilateral GPi-neurostimulation in a patient with Pisa-syndrome with a follow-up period of four years. The axial deformity decreased from 45 to 25 degrees with a relief from back pain [115].

A retrospective study analysed data from 101 patients with mild-to-severe trunk posture abnormalities of a cohort of 216 PD patients treated with STN-DBS. The independent effect of STN-DBS resulted in 41.4% improvement of abnormal trunk posture. The combined use of STN-DBS and levodopa resulted in 30.9% improvement [116].

A recent systematic review highlighted that parkinsonian camptocormia treated with DBS (89 patients underwent STN-DBS and 7 GPi-DBS) improved in 57 out of 96 patients (4.3-100% improvement) and remained stable or worsened in 39 out of 96 patients (2-100% worsening) [117]. Parkinsonian Pisa syndrome (11 patients underwent STN-DBS, 2 patients GPi-DBS and one patient unilateral pedunculopontine DBS) improved in 10 out of 14 patients (33.3–66.7% improvement) [117]. The non-parkinsonian camptocormia was treated with GPi-DBS and improved in all patients (50-100% improvement). Two patients with dystonic opisthotonos had an excellent response to GPi-DBS and there were variable responses in 3 patients with parkinsonian anterocollis after STN-DBS performed for motor fluctuations [117].

Outcomes for dystonia in Lesch-Nyhan disease, Wilson’s disease and Huntington’s disease are variable [47, 48, 64, 118-122]. Piedimonte et al. presented a patient with Lesch-Nyhan disease treated with bilateral GPi, who showed 60% improvement of BFMDRS score as well as Mean Disability Scale (MDS) score at 12 months follow up with complete disappearance of self-injurious behaviour. These therapeutic benefits were persistent at five year follow up [118].

Bilateral posterior subthalamic area-DBS has been effective in improving tremor as well as dystonic postures in a patient with Wilson’s Disease [120]. However, bilateral GPi might be the most indicated target if dystonia is the prominent clinical features or VIM-DBS if the disabling symptom is the tremor [119].

Bilateral GPi-DBS has showed beneficial input in a case series of Huntington’s Disease patients [121] producing an improvement of the motor part of the Unified Huntington's Disease Rating Scale (UHDRS) at six months postoperatively (- 17%). However, the effect was not sustained twelve months after the operation (- 5%) [121]. On the contrary, Gonzalez et al. found a sustained therapeutic effect of bilateral GPi-DBS with a mean improvement on the chorea subscore equal to 59.8% at 3-year follow up [122]

A multicentre retrospective study on 23 patients affected by neurodegeneration with brain iron accumulation (NBIA) (61% with PANK-mutation) treated with GPI-DBS demonstrated an early improvement (range: 2–6 months after surgery) by 28.5% (mean BFMDRS score compared with baseline) as well as an improvement of 25.7% at 9 to 15 months [123] with also an important benefit on the quality of life. In line with these results, a case-report concluded to maintained improvement of severe generalized dystonia after DBS in NBIA type 1 [124].

Dystonias caused by rare genetic abnormalities (atypical dopa-responsive dystonia, chorea-acanthocytosis, SCA 2, Wilson’s disease, methylmalonic aciduria etc.) treated with DBS –almost exclusively of GPi – concluded to a variable motor and disability improvement at 1-year follow-up [125].

1. **DBS IN STATUS DYSTONICUS**

A specific indication for DBS surgery is the status dystonicus (SD), a life- threatening condition that can lead to respiratory, metabolic and bulbar complications requiring in extremis intubation and ventilation . This may also occur in existing patients with GPi-DBS, who experience sudden failure of their system – usually due to battery failure. Medically refractory SD has been treated with thalamotomy [126], pallidotomy [127] and most recently GPi-DBS [128] with favourable outcomes.

The case-series of 5 paediatric patients with DYT1-dystonia and refractory SD treated with DBS reported a significant symptomatic relief (decrease of dystonic movements and resolution of abnormal postures) in 4 patients (1 remained stable) with extubating times being shorter than in other reports of patients treated with pharmacological options [129].

Furthermore, a review of 5 cases of early DBS for SD reported a significant relief with a median of 3 days (range 1-7) after surgery. There was no recurrence of SD in the last follow-up period [130]. Another retrospective study presented 40 patients receiving DBS and developing overall 58 SD-episodes. DBS was efficient in resolving 90% of these episodes [131].

1. **ELIGIBILITY AND PATIENTS’ SELECTION**

The decision making for or against DBS in each patient is the result of a multidisciplinary and complex assessment. The dystonia severity including functional impairment or social disability should influence the surgical decision. The natural history without surgical treatment should be assessed as well as the time course of the condition with medical treatments. The expected outcome from DBS can then be evaluated for comparison as well as the necessary morbidity; risks and any possible complications with their management should be discussed with the patient in order to predict the likely response profile to DBS [19].

In order to inform the patient, the presurgical workup should include genetic tests as some mutations have more favourable response to DBS than another (e.g. DYT1 has a better DBS-outcome than DYT6 [59]).

The dystonic phenotype should guide the decision. Indeed, patients with isolated dystonia predominantly affecting limbs, neck and trunk are usually good responders to the neurostimulation. The outcome in orofacial dystonia is less predictable [59, 132].  Patients with combined dystonia are less likely to benefit from DBS because of other coexistent motor symptoms (with the exception of myoclonus and sometimes tremor).

The evaluation of dystonia patients planned for DBS should include the identification of factors predicting a positive as well as a negative outcome (some particular types of dystonia, skeletal deformities, spasticity etc.) and risks of side effects. A levodopa trial is recommended in all patients with symptoms’ onset before age 21 years and considered in patients with dystonia onset before age 50 years to rule out levodopa-responsive dystonia. Tests for other pharmacologically treatable dystonias (e.g. Wilson disease) should be also performed. The appropriated doses of botulinum toxin should be optimised if indicated (e.g. in focal or segmental dystonia). Differentiating psychogenic from organic dystonia is essential, although sometimes difficult [64]. A brain MRI scan to rule out or to confirm some structural abnormalities should be preoperatively performed [63].

Screening for premorbid psychiatric symptoms or cognitive dysfunction is reasonable, keeping in mind that globus pallidus pars interna (GPi) DBS has been used successfully in psychiatric patients with tardive dystonia and in some patients with cognitive impairment [133-135].

Some other DBS outcome-predicting factors are currently investigated, e.g. the range of voluntary neck motility predicts [136] and the motor cortical plasticity [7].

Younger age, shorter disease duration and response to levodopa are considered to be predictive factors for the preferred outcome of STN-DBS from two class II studies [137].

BOX 1

Selection criteria for DBS in Dystonia

* Early age
* Short disease duration
* Presence of factors predictive of a positive (e.g. DYT1 mutation) response
* Failure of Levodopa Trial
* Failure of Botulinum Toxin Injections
* Negative genetic tests for diseases completely treatable (e.g. Wilson’s Disease)
* Exclusion of psychogenic dystonia
* Exclusion of fixed skeletal deformities, spasticity and myelopathy
* Exclusion of severe brain damage

1. **DIFFERENT TARGETS**

The commonest target for DBS in dystonia is the posteroventral lateral portion of the GPi. This popularity is due to positive outcomes after pallidotomy in this area [138, 139].

In 20 cervical dystonia patients was demonstrated that the centroid of highly clinically beneficial stimulation was about 2-3 mm above the ventral border of the lateral posteroventral GPi [140]. The most effective contact position in DYT1 patients with GPi-DBS was found relative to mid-commissural point at 20.2±1.5 mm lateral, 3.0±1.6 mm anterior and 0.7±2.4 mm dorsal [141].

Recent evidences suggested that STN-DBS can also be effective in patients with generalized or focal (cervical) dystonia [24, 142] with lesser bradykinesia or freezing of gait side effects [13, 24, 143]. Moreover, the stimulation parameters for STN are lower than those used for the GPi, resulting in longer battery life [24].

A single‐centre prospective double‐blind crossover study comparing the efficacy of bilateral GPi‐DBS and STN‐DBS for the treatment of isolated dystonias demonstrated no superiority in clinical efficacy between the two targets, although STN stimulation patients had a slight better scores than those receiving GPi stimulation (BFMDRS motor score improvement: 13.8% vs. 9.1%) [23].

Another retrospective study showed at 1-month follow-up a significant difference in BFMDRS total movement score improvement (p = 0.01) in case of STN-DBS (64%) than of GPi-DBS (48%) but not at 6 and 12 months follow-up. At 12-month follow-up, the improvement in the axis subscore was significantly (p = 0.03) larger in case of GPi-DBS (93%) than after STN-DBS (83%). The authors concluded that GPi and STN DBS were effective in alleviating dystonia. However, GPi stimulation might be better for reducing axial symptoms [144].

A pooled meta-analysis of GPi and STN DBS outcomes for cervical dystonia showed as well no difference between these targets with a significant improvement of the dystonic symptoms based on TWSTRS scores (39 studies, mean follow-up: 23,3 months). The percentage of responders was 89% for both stimulated nuclei. The adverse effect profiles of the targets were different [145].

Taken together, the current studies support effectiveness and long-term tolerability of STN-DBS in dystonia, although larger comparative studies with GPi are needed.

The thalamus was the first target to treat dystonia, although it was quickly overtaken by the GPi years later [146]. On the other hand, Vim-DBS has been shown to provide relief of dystonic tremor in several patients but not in patients with pure dystonic postures. A recent retrospective study demonstrated an initial improvement of 41% 12 months after surgery, although it was not sustained in the long-term follow up [147].

Regarding patients with more phasic or tonic components rather than dystonic tremor, DBS in more anterior regions of the ventral thalamus such as the ventralis oralis posterior nucleus (Vop) and the ventralis oralis anterior nucleus (Voa) can be considered [148].

Due to its important connections with cortical and subcortical structures, the cerebellum has emerged as a promising target for neuromodulation in neurological disorders [149, 150], patients with spasticity and dystonia secondary to CPunderwent a deep anterior cerebellar lobe DBS with 25% improvement in dystonia in five of them [21].

The EFNS guidelines [151] recommended DBS of GPi as a good option for idiopathic generalized and segmental dystonia (Level A) and for cervical dystonia (Level B). For acquired dystonia, pallidal DBS is less effective (Level C). The AAN guidelines for tardive dystonia [152] concluded that there was insufficient data to recommend DBS to control tardive dystonia.

1. **SIDE EFFECTS**

All patients undergoing DBS are exposed to risks; these may be categorised as stimulation related, hardware related and surgical side effects. Some conditions (e.g. CP or stroke) causing dystonia might have a high rate of complications because of comorbidities.

Although strictly not a risk, the failure of the procedure may be counted here. Statistically this might be the highest “risk” – this will depend on the pre-operative analysis of dystonia phenotype.

Stimulation-related side effects are due to the anatomical position of the DBS target. The “motor part” of GPi corresponds to the posteroventral lateral portion and is more effective for dystonia reduction compared with anterodorsally positioned electrodes [153]. However, the proximity of optimal stimulation volume to the internal capsule is challenging as the excessive current can spread into corticospinal or corticobulbar fibres and cause motor side effects [103, 154] as dysarthria, mild bradykinesia, gait freezing and even a full parkinsonian triad. The optic tract lies immediately below the GPi target; in this region stimulation can cause “uncomfortable” sensations to the patient.

Dysarthria is a frequent side effect due to stimulation. It was reported that 5 out of 117 cases developed immediate and completely reversible dysarthria with different stimulation parameters.

A reversible dysphagia was described only in one case [103].

A study on 15 patients with predominant torticollis and GPi-DBS provided evidence that speech impairment is not a frequent side-effect of GPi-DBS in primary dystonia, although stuttering and a worsening of dysarthria may be seen in individual patients [155].

In a trial of DBS for focal cervical dystonia, side–effects occurred in 26% and in 8% failed to resolve; the common ones related to stimulation were dysarthria and parkinsonism [140]. In other studies mild‐to‐moderate dysarthria and re‐occurrence of dystonic symptoms were the most common adverse effects (approximately 5%) corrected by stimulation parameters adaptation [156, 157].

Other commonly reported side-effects due to the stimulation were gait and balance impairment [96, 158, 159].Finger bradykinesia and hypokinetic gait disturbance with freezing of gait might occur in dystonia patients, even in unaffected limbs [136, 158, 160, 161].

Compared with GPi‐DBS, the spectrum of side effects is usually different after STN‐DBS and commonly includes (transient) dyskinesia, relevant weight gain and (transient) depression [143]

Hardware-related complications include infections, lead migration, fracture or failure of the lead and skin erosions. These complications usually require further surgical procedures. Their rate varies among the studies and can be as frequent as 25% according to a recent systematic review [162]. In dystonia, the hardware complications were reported to be higher than PD, probably reflecting the risk of the abnormal head/neck position that can expose the hardware to twisting forces [160].

Other side effects related to the device were reported by Damier et al. [97]. The cable connection exerted painful traction in a patient and the stimulator had to be fixed to the clavicle. In another case, the lead had to be re-implanted after 2 months. Some cases of infection at the chest pulse generation resolved after antibiotics [163-165].

The main surgical risks include intracranial haemorrhages (approximately 3% for all DBS patients [based on data for PD and tremor patients] and 2.7% for DBS dystonia patients [only 1 case out of 37 dystonia patients in a 10 years-retrospective study]) [165], as well as brain lesions with neurological dysfunctions (for all DBS cases approximately 1%).

The rates of hardware infection or malfunctioning requiring rehospitalization are variable but can be as high as 10% [64]. Only 1 case out of 117 had a venous infarction during lead placement without sequela in patients with refractory tardive dystonia [163].

Infection related to the extension leads or pulse generation were reported [163-165]; it is controversial if antibiotics alone without hardware removal is a successful treatment option.

Although not a side effect or risk, GPi-DBS is usually associated with high energy consumption leading to more frequent battery changes or with rechargeable devices shorter recharging intervals.

1. **NON-MOTOR OUTCOMES**

Dystonia is frequently associated with some non-motor symptoms such as pain and neuropsychological changes. Non-motor symptoms in dystonia syndromes were addressed by few studies and the results were contradictory. A marked improvement in pain score and depression after GPi-DBS in cervical dystonia was reported in two studies [166, 167]. However, significant decline in verbal fluency in one patient and in verbal memory in another was reported [166]. These results were not confirmed in another study [167]. A reduction in word fluency 12 months after surgery for cervical dystonia was attested by a multicentrical trial [168]. A patient with myoclonus-dystonica was reported developing depression and increase in obsessional-compulsive symptoms [169].

A study of 12 patients with isolated focal or segmental dystonia demonstrated improvements in working memory, executive function, anxiety and depression [170]. No significant changes after surgery were detected in a long-term neuropsychiatric outcomes in 57 patients with inherited or acquired, isolated or combined dystonia (mean follow-up = 24.4 ± 19.6 months) [171] supporting psychiatric stability of dystonic patients treated with GPi-DBS.

Considering the high psychiatric morbidity in the dystonia population, neuropsychiatric assessment is recommended pre- and post-operatively [20].

A systematic review of 52 studies reported significant reduction by DBS of pain related to dystonia both on short (6 months) and long-term follow-up (up to 6 year). The majority of patients did not experience onset or worsening of depressive symptoms. No major effects on anxiety, mood and cognition were found [172]. Three case series reported a trend to decrease between 28 and 59% in depression scores. In a case series of 93 patients with cervical dystonia, no difference in global cognition scores were found between baseline and post-operative condition with only a small decline in verbal memory and fluency of uncertain clinical relevance.

Psychiatric outcomes were stable in 13 cervical dystonia patients treated with STN-DBS and presented an improvement on anxiety and depression scales in 10 tardive dystonia patients [172].

Non-motor outcomes of thalamic-DBS were described in patients with dystonic tremor or myoclonus dystonia. Indeed, 7 cervical dystonia patients with head tremor stimulated in the thalamus/subthalamic area reported 90 % pain improvement [173, 174]. 7 patients with myoclonus dystonia treated with combined GPi-Vim stimulation showed no differences in affection and/or cognition (with GPi, Vim or both targets) [90].

1. **QUALITY OF LIFE IMPROVEMENT**

A systematic review of 36 articles involving 610 patients (21 articles on inherited or idiopathic isolated dystonia, 5 on tardive dystonia, 3 on CP, 2 on myoclonus-dystonia, 1 on X-linked dystonia-parkinsonism and 3 on mixed cohorts of different dystonia subtypes) found a significant improvement in physical quality of life (QoL), whereas gains in mental QoL were less robust and likely related to the complexity of associated neuropsychiatric comorbidities [144].

A long-term (over 10 years) investigation of 37 patients concluded to a sustained QoL improvement [175]. A nine-year study highlighted a significant correlation of changes in health-related QoL with changes in motor outcomes (R2 = 0.384, p = 0.010). The short-term motor and health-related  QoL improvements predicted long-term outcomes [176].

In a prospective study, despite improvement in QoL (Physical and Mental Component improved by 32.42% and 29.46% respectively), patients showed no significant change in anxiety and depression status [177].

1. **MECHANISM OF ACTION**

Isolated dystonia is considered nowadays to be due to an impairment of a wide network of brain areas including motor cortex, basal ganglia, cerebellum and brainstem [178, 179]. Animal models of dystonia phenotypes support the involvement of basal ganglia and sensorimotor triggers in dystonia [180]. Studying the genes, animal models and pathophysiology of dystonia has provided more knowledges about this syndrome. However, there is still an important gap in translating these studies’ results into an understanding of motor control changes, which underlies dystonic symptoms [180]. Abnormalities in sensorimotor integration and loss of surround inhibition in the cortex was found as the main neurophysiological mechanisms underlying dystonia [181]. In addition, alterations in neuroplasticity at cortical as well as brainstem level were found as a key neurophysiological phenomenon underlying dystonia [182].

Overall, idiopathic and genetic dystonias appear to be neurofunctional disorders with no apparent neuron loss [180]. In acquired dystonias, the symptoms can result from brain damage through various causes and usually point to basal ganglia as a pivotal brain region [180].

Due to limited knowledges about the pathophysiology of dystonia, the understanding of mechanisms underlying DBS-efficacy is also limited. GPi is the primary output of basal ganglia [58]. Imaging studies revealed that the main functional effect of GPi-DBS is to normalize pathologically overactive motor activation responses and patterns in these patients [67, 183]

It is also thought that DBS increases output from GPi and activates surrounding fibre pathways, resulting in a complex pattern of modulatory effects on the entire basal ganglia thalamocortical network [184].

Recordings of GPi neuronal activity obtained from implanted DYT1 patients demonstrated an abnormal firing pattern with an excess of synchronization in the low-frequency band [185]. This abnormal oscillatory activity within GPi might be the expression of an aberrant plasticity distorting network function [182].

The fact that clinical response to DBS is delayed for days or weeks and some patients may not experience a return of symptoms for prolonged periods of time after stimulation ceases might support the hypothesis that DBS induces unknown neuroplastic changes [63].

DBS might act in neurochemical systems but studies exclusively on dystonia are lacking [186].

The stimulation-induced regularization of neuronal patterns prevents transmission of pathologic bursting and oscillatory activity within the network. Therefore, the processing of sensorimotor information improves and clinical symptoms decrease [187, 188].

1. **CONCLUSION AND FUTURE DIRECTIONS**

Interleaving stimulation (ILS) iprovides individualized stimulation of 2 contacts delivering in alternating order. Only marginal effects were evident in a cohort of 7 patients [189].

Adaptative DBS (aDBS) is an experimental technology depending on different characteristics of pathological oscillations within the cortico-basal ganglia-thalamo-cortical network. It has been already used in PD and is currently being investigated in dystonia. However, large studies as well as common clinical implementation are still lacking [33].

A key factor to minimize DBS-induced side effects is to avoid stimulating structures and brain regions involved in adverse events. A major advance toward this objective is the use of directional leads, which may deviate and steer current away from these structures.

Directional DBS (dDBS) has been already used in PD [190]. Further research studies are necessary to explore the benefit of dDBS in dystonia patients.

Combining anatomical programming (MR scanning to show the true position of an electrode relative to nuclei – i.e. GPi) with physiological programming (local fields potential) might be the key for improving the DBS outcome in dystonia, especially complex phenotypes. Are anatomical and neurophysiological programming consistent? Testing this research question might help to discover further useful DBS targets for dystonia.

A recent multicentre i study identified location and volume of tissue activated (VTA) as the most important factor for the therapeutic efficacy of DBS in dystonia and provided the most effective stereotactic coordinates [191].

Computational models may assist lead positioning and programming and provide more consistent outcomes in the future [192]. A critical aspect is patient selection for DB and further studies are necessary to develop a consensus on selection criteria for dystonia [192]

Further studies are necessary to identify the optimum timing of stimulation to answer to the following question: when is it refractory? In addition, it would be intriguing to discover the reasons behind the delay in responding to DBS from dystonic postures. What is the neurophysiological process that takes time after starting the stimulation?

Advancements in neuroimaging and neurophysiological techniques have been instrumental in defining these structures in order to refine the therapy, optimise efficacy and minimise side effects. However, there are still several unmet needs to investigate in the future years.

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