Deep Brain stimulation in the Treatment of Dystonia – The Importance of Patient Selection

Introduction

Dystonias are a heterogenous group of debilitating disorders affecting children and adults. They are characterised by involuntary concurrent muscle contractions of antagonistic pairs leading to twisting and writhing body postures.[1] Movements vary in speed and duration and depend on the activity or posture adopted by the patient; in extreme cases they can become fixed.[1] Deep brain stimulation(DBS) is a neurosurgical procedure for movement disorders and this essay intends to assess its role in the treatment of dystonia.

Classification of Dystonias

Classifying dystonia is challenging due to the heterogeneous nature of the disorder and can be based on a number of parameters. Primary dystonias occur spontaneously without obvious cause and are not associated with other neurological pathologies, except occasionally tremor and myoclonus. They are often due to hereditary aetiology(Fig.1).[1-2] Cases of dystonia that manifest at an early age are rarer, often have a clear genetic basis and are more likely to progress to

Designation	Dystonia type	Mode of inheritance
DYT1	Early-onset generalized torsion dystonia (dystonia musculorum deformans, Oppenheim's disease)	Autosomal dominant
DYT2	Autosomal recessive torsion dystonia	Autosomal recessive
DYT3	Dystonia-parkinsonism ("lubag")	X-linked recessive
DYT4	'Non-DYT1' dystonia (whispering dysphonia)	Autosomal dominant
DYT5	Dopa-responsive dystonia (DRD)	Autosomal dominant (Segawa) Autosomal recessive (DRD)
DYT6	Adolescent-onset dystonia of mixed type	Autosomal dominant
DYT7	Adult-onset focal dystonia	Autosomal dominant
DYT8	Paroxysmal non-kinesigenic dyskinesia	Autosomal dominant
DYT9	Paroxysmal choreoathetosis with episodic ataxia and spasticity	Autosomal dominant
DYT10	Paroxysmal kinesigenic choreoathetosis	Autosomal dominant
DYT11	Myoclonus dystonia	Autosomal dominant (maternal imprinting)
DYT12	Rapid-onset dystonia-parkinsonism	Autosomal dominant
DYT13	Multifocal/segmental dystonia	Autosomal dominant
DYT15	Myoclonus dystonia	Autosomal dominant

Fig.1: The genetic basis of primary dystonias and their modes of inheritance. Adapted from Breakefield et al.[2]

affect the whole body(general dystonias).[1-2] Those of later presentation also have a genetic basis although are commoner and more often focal non-progressive dystonias. Examples include cervical(torticollis), blepharospasm, oromandibular, laryngeal(spastic dysphonia) and hand or foot dystonias.

In contrast, secondary dystonias have an attributable cause and often occur with other neurological features.[2] Hence, clinical symptoms are hugely varied and will depend on the underlying nature of the dystonia. Many causes have been described and include traumatic, vascular, infectious, neurodegenerative, metabolic and pharmacological (tardive dystonias).[2]

Clinically, topological symptoms can also direct classification; segmental dystonias involve two or more adjacent regions and multifocal dystonias involve two or more non-adjacent regions.[1-3] Hemidystonias affect one half of the body, whereas generalised dystonias exhibit a broader distribution.[1-3]

Medical Treatments

Classification in practice is of great importance in directing therapeutic options that will provide the greatest benefit for the individual patient(Fig.2). Currently first-line treatment options for generalised dystonias are medical, including antidopaminergics, anticholinergics and $GABA_B$ agonists(Fig.3).[1,4-7] It has been hypothesised that impaired inhibition in various areas of the nervous system fails to supress neuronal excitability and this may lead to aberrant activation of circuitry causing involuntary contraction of muscles and also 'overflow activation' of adjacent muscles.[1-2,4] Abnormal activity has indeed been described in the basal ganglia.[8-9] Medical therapy targets this aberrant activity by altering various neurotansmitters involved.

Drugs can also induce movement disorders and so give an insight into the molecular pathways involved. Levadopa use in Parkinson's disease can cause dystonic movements but conversely is therapeutic in a small subset of dystonias (Segawa's/dopa-resposive dystonias).[1,5] Moreover, dopamine receptor antagonistic anti-psychotics can cause dystonic symptoms(tardive dyskinesias).[1]

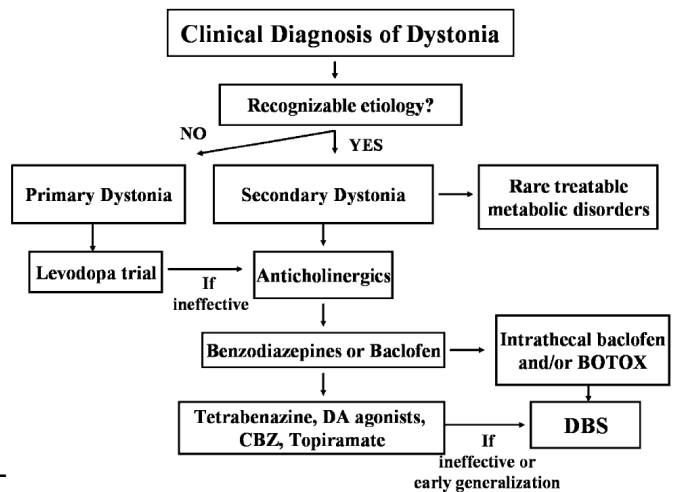*Fig.2: An algorithm for the treatment of dystonias. [DA = Dopamine; CBZ = Carbamazepine; DBS = Deep Brain Stimulation] Adapted from Alterman et al.[4]*

Another front-line therapy is Botulinum toxin, which has a role in focal or segmental dystonias and indeed is considered first line therapy in idiopathic cervical dystonia(Fig.3).[5-6] It selectively blocks the cholinergic innervation of striated and smooth muscles.

Fig.3: Table showing the treatment options depending on the classification of dystonia. [BoNT = botulinum neurotoxin; DBS = Deep Brain Stimulation] Adapted from Delnooz et al.[5]

Type of Dystonia	First-line treatment	Second-line Treatment	Refractory cases
Generalised	Trihexyphenidyl	BoNT Baclofen Clonazepam	Pallidal DBS Tetrabenzine/neuroleptics Intrathecal Baclofen
Spasmodic	BoNT		Myectomy
Cervical	BoNT	Trihexyphenidyl Baclofen Clonazepam	Tetrabenzine Pallidal DBS Selective peripheral denervation
Blepharospasm	BoNT	Baclofen Clonazepam	DBS Myectomy
Oromandibular	BoNT	Baclofen Clonazepam Tetrabenzine	
Focal hand	BoNT		

What is Deep Brain Stimulation?

DBS is considered as a treatment option for medically refractive dystonias.[1-7] DBS involves neurosurgical placement of electrodes in the Globus pallidus internus(GPi) of the basal ganglia, an area in the brain governing movement.[10-11] Historically ablative therapies were used for movement disorders; however, stimulation has superseded this, as it is a non-destructive, reversible and adjustable technique.[12] Therefore, it can be used bilaterally without risk of unwanted damage to key areas involved in language, movement and cognition.[10-12] Certain criteria are necessitated for use of DBS, including an unequivocal diagnosis of dystonia, irresponsiveness to medical therapy and a significant disability warranting the use of surgical intervention in the face of associated potential risks.[1] The optimal patients have not had dystonic symptoms for a prolonged period of time, as the onset of orthopaedic deformities that are irreversible will limit function even if the surgery provides symptomatic cure.[4]

The DBS device consists of a lead with attached electrodes which is implanted within the deep brain target, it is attached to an intervening extension cable that leads to a programmable pulse generator(PG), which delivers the therapeutic current and is implanted in the chest wall.[1,4,11] The device is implanted in two stages. First the lead is implanted into the GPi and then the cable and PG are implanted. Electrodes are implanted under the use of stereotactic navigation systems using imaging-guided systems for anatomical mapping and an intraoperative microelectrode recording(MER) can be used for electrophysiological mapping. If using MER dystonia medications are withheld on the day of the surgery to prevent interference.[4]

The patient is either awake, to monitor neurological status, or under general anaesthesia during the operation. Awake-surgery may not be possible due to the symptoms of

dystonia and the decision is based on this and other considerations. Intra-operatively the location of the electrode is optimised and subsequently tested to ensure that unacceptable side effects do not occur and to check thresholds for stimulation. The electrode is generally placed in the posterior GPi in treatment of dystonia.[1,4,10-11]

The device is activated 7-10 days postoperatively to allow the surgical incisions to heal. The PG can be adjusted transcutaneously, with amplitude, pulse-width, frequency, and choice of the active contacts programmable.[7] Settings are not standardized and often patients require optimization during post-operative care with varying evidence of optimal parameters. Unlike in Parkinson's disease where there is often immediate impact, in dystonia improvement occurs gradually over a number of months.[7]

Most centres report use of wide pulse-widths (210–400µs) and high frequencies (over 130Hz) with good results.[4] However, Vercueil *et al* assessed the effects of bilateral pallidal stimulation at short (60–90µs), medium (120–150µs) and long (450µs) pulse-widths in 20 patients six month post-operatively.[13] Analysis demonstrated no significant difference in outcome. Thus, shorter pulse-widths can be used chronically to save stimulator energy and may even reduce adverse effects of higher delivery, such as motor tonic contraction and visual flashes, and allowing longer time before replacement of hardware and batteries.[4,14-15]

In the paediatric population special considerations must be taken into account. The skull growth of a child can increase the risk of lead migration and damage to the hardware. However, by the age of seven, this issue is not so problematic and can be minimized by use of extra device length, accommodating additional expansion.[11]

Complications of DBS

Overall intra-operative complication rates are low; one neurosurgical centre reported only 12 procedural complications whilst using DBS over seven-years and 106 operations.[16] These include a 1-2% risk of haemorrhagic stroke, 5% risk of infection and a 1% risk of lead fracture per year post-operatively, although this is greater (up to 18.4%) in idiopathic cervical dystonia due to the increased stress put on the hardware by dystonic neck movements.[17-18] Problems with migration of electrodes post-operatively can hinder outcome; poor lead positioning occurs independent of surgical experience in 2% of DBS procedures and may necessitate revision.[19] However, techniques have been developed to allow easy access for revision of placement to 'fix' the DBS lead and improve safety of the procedure.[20]

Post-operatively common complications include dysarthria, dysphonia and stuttering.[11,21-23] Also reported are poor co-ordination, akinesia and bradykinesia, gait difficulties, paraesthesias, abnormalities of posture, laughter and lethargy.[15,19] Suicide has been noted as a side effect of DBS; however, the true nature of this correlation is complex and indeed in one study by Foncke *et al* two patients that committed suicide had symptoms of depression pre-operatively.[24]

The Importance of Patient Selection

Contraindications to the use of DBS include conditions that will increase intra-operative risk such as bleeding diathesis or anti-platelet therapy that cannot be temporarily discontinued.[11] Patients with susceptibility to infection may also be poor candidates but these factors need to be balanced against the potential benefits of the procedure and the patient and physicians considerations.[11]

Patient selection is vital and prior to undergoing the operation patients should be screened for cognitive disorders such as dementia, as this is a potential complication of DBS. Furthermore, the patients' current physical function and expectations should be determined to assess specific requirements for rehabilitation and in order to set realistic goals. However, all such factors are considered on an individual basis and require consideration of the potential risks and benefits of the intervention.[11,19,25]

DBS surgery is expensive, costing in the range of $75-150,000 and probably more owing to post-operative care and subsequent maintenance of hardware (including replacement of worn-out batteries and generators) every few years.[11,14] Nevertheless, this must be balanced against the huge benefits seen in many patients symptomatically and more importantly in quality of life. Importantly, the long term safety and efficacy of DBS has been evaluated with good results,[26-29] one study demonstrated efficacy even at nine years post-implantation,[27] and so the positive impact on quality of life is maintained.
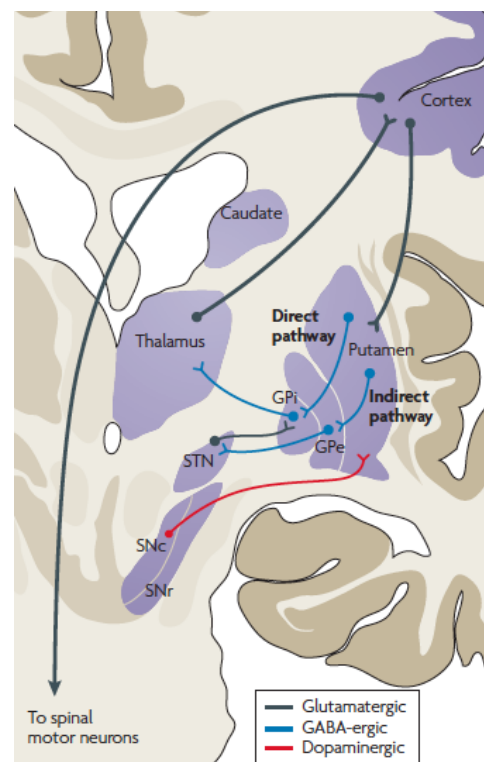

Fig.4: Schematic of neuro-circuitry of the Basal Ganglia. [STN = Subthalamic Nucleus; SN = Substantia Nigra (showing pars reticula and pars compacta); GPi = Globus Pallidus Internus; GPe = Globus Pallidus Externus] Adapted from Breakefield et al.[2]

Pathophysiology underlying Dystonia

The GPi is the major output nucleus of the basal ganglia projecting to the ventrolateral thalamus with downstream effects in the supplementary motor cortex(Fig.4).[2] Evidence points to abnormal activity of the GPi in dystonia and theory is that DBS attempts to restore normal activity here by

over-riding the pathological bursting of neuronal subsets.[2,4,11]

However, this does not explain why symptomatic improvement is progressive after procedure and also why when the stimulation is turned off relapse of symptoms is delayed. GPi DBS has diffuse effects within the brain; functional imaging studies have shown a reduction in hypermetabolism in supplementary motor areas after treatment with DBS, thought to be due to this modulating activity at the GPi(Fig.5).[30-31] *In vivo* imaging of patients with primary and secondary dystonias show similar sensorimotor abnormalities but it is unknown as to whether these are secondary to the dystonia or due to compensatory mechanisms.[2] Nevertheless, regular stimulation by the DBS may prevent downstream effects that trigger dystonic symptoms.
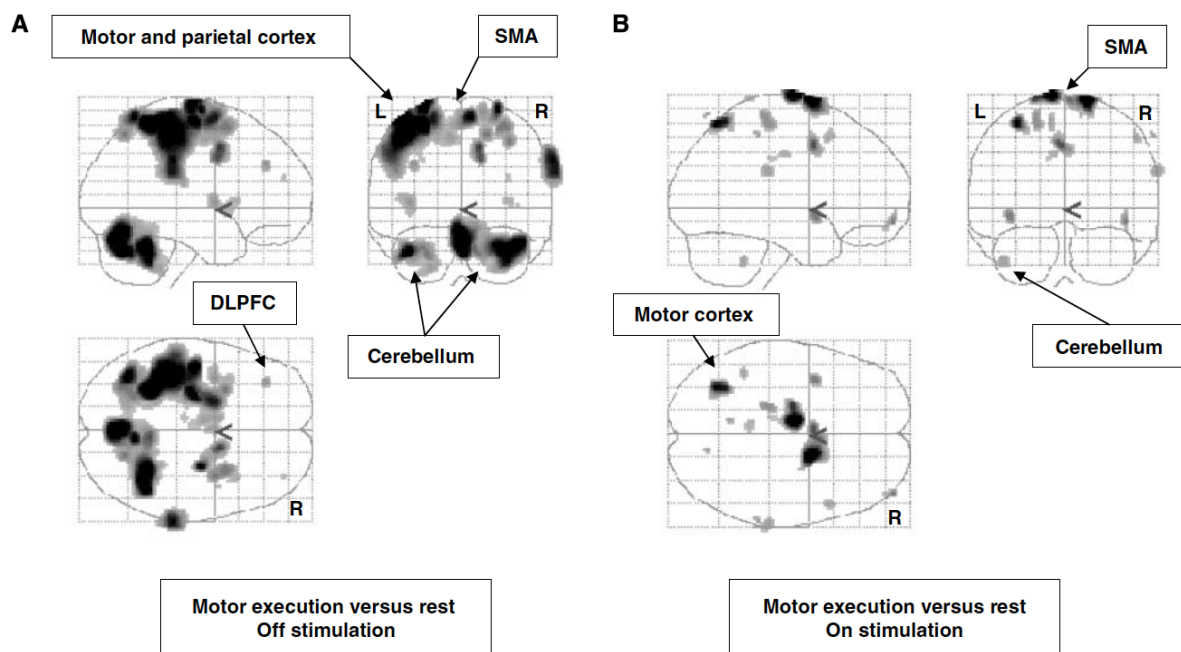

Fig.5: Sagittal, lateral and coronal views of Positon Emission Topography results showing pattern of activation during motor execution versus rest when the Deep Brain Stimulation is turned off (A) and on (B) in five patient with tardive dyskinesia. [SMA = Supplementary Motor Area; DLPFC = Dorsolateral Prefrontal Cortex] Adapted from Thobois et al.[30]

Questions remain; understanding of how the DBS affects neural tissue surrounding the electrode and the neural circuitry of movement will be key to future developments. Local unwanted effects, including changes in mood, memory, impulsivity and hallucinations suggest that effects of DBS are widespread.[10] Knowledge of the normal pathways and the abnormal causes of dystonias will aid more precise targeting of stimulation. Indeed, targeting other areas may be beneficial; for example, unlike generalized dystonias, occupational dystonias appear to be sensitive to thalamic surgery, suggesting separate pathophysiology.

Evidence Supporting Use of DBS in Primary Dystonia

For focal generalised dystonia the degree of improvement after DBS ranges hugely between studies from 21-95%; most being at 60-70%. Vidailhet *et al.* studied 22 patients with primary generalized dystonia over a year and reported a mean improvement of 54% in the Burke-Fahn-Marsden Dystonia Rating Scale-motor (BFMDRS) movement score and 44% in the BFMDRS-disability score.[32] The presence of fixed postures such as severe torticollis or scoliosis limited improvement in some patients. At 3 years these improvements remained constant and a improvement in function and quality of life was reported.[33] Kupsch *et al.* reported a series of 40 patients with primary segmental and primary generalized dystonia treated with bilateral GPi DBS with randomization to either neurostimulation or sham stimulation for 3 months.[34] Those receiving neurostimulation had a mean improvement of 39.9% in BFMDRS movement scores and 38% in BFMDRS-disability scores, compared with 4.9% and 11% in the sham group.[34]

One study of dystonia with young-onset primary DYT1 dystonia showed a shorter duration of disease, at time of bilateral GPi DBS, correlated with better functional outcomes.[35] These results display the importance of early diagnosis and referral to the

surgical team if refractory to medical therapy. Initially, evidence suggested that a mutation in the DYT1 gene underlying generalized dystonia, predicted a better response to DBS treatment,[36-37] but this has not been replicated in other studies, requiring further investigation.[32-34]

The posterior part of the ventrolateral thalamic nucleus has also been targeted in primary generalized dystonia and two of three patients experienced a 'mild-to-moderate' improvement in limb dystonia, although axial symptoms were unchanged, more research is needed to assess potential of areas other than the GPi to target in DBS.[5,38]

Evidence Supporting Use of DBS in Secondary Dystonia

The use of DBS in treating severe, medically refractory primary generalized dystonia has been proven but it is still not yet clear whether the same benefits are seen with secondary dystonias.[7,39-40] Assessing success in treatment of secondary dystonias is difficult due to the heterogeneity of the underlying cause and difficulty in assessing large number of similar patients in a single neurosurgical centre. Generally it is noted that patients with secondary dystonia respond more modestly and inconsistently than those with primary dystonia.[11,23,34,40] Patients with dystonia secondary to ischaemic injury that have preserved function of the basal ganglia respond better to DBS than other secondary causes and, as previously mentioned, this may be due to the more diffuse damage resultant of other underlying causes.[4]

Comparative studies of primary and secondary dystonia have also shown this discrepancy. In one such study, fifteen patients with dystonia had either pallidotomy DBS.[41] Nine patients with primary dystonia (generalized and cervical) responded much

better than the other six with secondary dystonia (generalized, segmental, and hemidystonias). There was no correlative difference between the pallidotomy and DBS. The authors did note that the presence of 'basal ganglia abnormalities on the preoperative magnetic resonance imaging scan is an indicator of a lesser response to pallidal interventions for dystonia.'[41]

However, Castelnau *et al.* reported six patients with the hereditary degenerative syndrome, pantothenate kinase-associated neurodegeneration (PKAN), demonstrating a 75% mean improvement in BFMDRS movement scores, with follow-up from 6 to 42 months.[42] There have also been a number of trials evaluating the use of DBS in tardive dystonia, all showing some improvement in BFMDRS movement scores (range, 35%–73%). It is also reported that in such cases the movement disorder is very rapid in contrast to DBS in other subsets of dystonia.[11]

Therefore, DBS is clearly of use in a number of types of secondary dystonia but understanding which types remains unclear. Single-photon emission computed tomography (SPECT) imaging analysis shows reduced perfusion after DBS in the primary motor cortex, premotor and supplementary motor cortex, and prefrontal cortex.[43] DBS may be less effective in some secondary dystonias due to irreversible tissue damage outside of the basal ganglia. This highlights the importance of functional neural circuitry in the brain that is a requisite for success in DBS. Hence, SPECT imaging may have a role clinically in deciding which patients are ideal for this surgical intervention.[43]

Evidence Supporting Use of DBS in Focal Dystonia

DBS treatment of idiopathic cervical dystonia has had good results, ranging from 43% to 76% improvement in Toronto-Western-Spasmodic-Torticollis Rating Scale(TWSTRS).[6,43] One Canadian study of 10 patients with medically refractory cervical dystonia showed a 44%, 64%, and 65% mean improvement in severity, disability, and pain scores one year post-operatively.[44] Importantly quality of life, measured by the SF-36 survey, also improved from 90.9 pre-operatively to 112.9.[44] A similar study in 2009 showed that in 10 patients undergoing bilateral GPi DBS all but 1 showed at least 25% improvement on all subscale scores of the TWSTRS and 7 more than 50%.[28] Two patients had a complete restoration of neck positioning, movement and were pain free. Overall most patients had an improvement in position and movement but still experienced pain.[28] The most long term study of cervical dystonia, by Hung *et al*. showed these good outcomes were maintained at 3 years.[29]

The successful use of DBS in cervical dystonia has led to increased experimental use in other forms of focal dystonias. DBS has been shown to benefit blepharospasm & oromandibular dystonia when used in Meige's syndrome; however, there is insufficient evidence for its use non-syndromatically.[6] Other areas have also been targeted in focal dystonias; one study reported on nine patients with cervical dystonia were treated with DBS at the subthalamic nucleus(STN).[45] Results showed improvement by 37% on the TWSTRS total score at 12 months. Quality of life measures also improved and STN-DBS caused no cognitive side effects or Parkinsonism.[45] Thalamic DBS and thalamotomy have also shown some benefit in focal hand dystonia.[6]

The Role of Stereotactic Surgery

Gross *et al* suggest that there is an overestimation of the usefulness of DBS and that evidence for use of stereotactic surgery may be underestimated due to improvements in technical aspects since large-scale studies evaluated its efficacy.[46] Pallidotomy remains a useful alternative in situations where DBS is not available or not possible. Furthermore, lesioning may also be used in combination with DBS. A small study of patients with secondary dystonia due to cerebral palsy assessed use of bilateral GPi DBS plus unilateral ventralis oralis thalamotomy in six patients versus bilateral GPi DBS in four.[47] Results showed a similar improvement in movement(32%) but that those having had thalamotomy had improved disability scores(14.3% vs 0.18%).[47] The study also assessed focal dystonias of secondary nature (including: post-traumatic, metabolic, genetic, or secondary to neuroleptic medication) with impressive results for bilateral GPi DBS, 77.7% improvement in movement and 80% in disability scores.[47] This discrepancy highlights the difficulty of treating secondary dystonias that are attributable to a more diffuse pathology. A deeper understanding of the normal pathophysiology of the movement circuits and the pathological sequelae of cerebral palsy and other such causes of secondary dystonia is necessary to target the correct combination of anatomical areas so that functional outcome can be maximised on an individual case basis.

Future Directions for DBS

Technological advances in the DBS system should provide improvements of therapeutical value. Current systems are open-loop which do not respond to local oscillatory feedback networks and so a greater understanding of electrophysiology of circuits involved could provide the basis for closed loop systems that would deliver stimulating currents based on the local electrical activity.[48-49] Improvements are also

needed postoperatively in programming the adjustable system to optimise performance and reduce associated problems. This could even be done remotely to ameliorate post-operative care of the patients.[47] Non-invasive transcortical approaches are also being used experimentally and may provide another treatment option in movement disorders in the future.[50]

Conclusion

In conclusion, the programmable nature of DBS has allowed ethical long term randomised and blinded control trials to assess efficacy, and evidence shows that DBS is an effective treatment for primary and a number of secondary dystonias, depending on the underlying cause. Identifying the best surgical candidates is pivotal in ensuring the best outcomes possible for the individual patient are met. Understanding the electrophysiological and neuroanatomical basis of the heterogeneous secondary dystonias may provide opportunities to use DBS in other sites with potential for improved functional outcome and quality of life. Although, DBS is currently a fantastic treatment modality when used in the correct patient subset, it is hoped that technological advances may provide novel therapeutic avenues in the treatment of dystonia.

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