

A practical guide to troubleshooting pallidal deep brain stimulation issues in patients with dystonia

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Abstract

High frequency deep brain stimulation (DBS) of the internal portion of the globus pallidus has, in the last two decades, become a mainstream therapy for the management of medically-refractory dystonia syndromes. Such increasing uptake places an onus on movement disorder physicians to become familiar with this treatment modality, in particular optimal patient selection for the procedure and how to troubleshoot problems relating to sub-optimal efficacy and manage therapy-related side effects.

Deep brain stimulation for dystonic conditions presents some unique challenges. For example, the frequent lack of immediate change in clinical status following stimulation alterations means that programming often relies on personal experience and local practice rather than real-time indicators of efficacy. Further, dystonia is a highly heterogeneous disorder, making the development of unifying guidelines and programming algorithms for DBS in this population difficult. Consequently, physicians may feel less confident in managing DBS for dystonia as compared to other indications e.g. Parkinson's disease.

In this review, we integrate our years of personal experience with the programming of DBS systems for dystonia with a critical appraisal of the literature to produce a practical guide for troubleshooting common issues encountered in patients with dystonia treated with DBS, in the hope of improving the care for these patients.

Introduction

Dystonia is the third commonest movement disorder worldwide. It is typified by its motor manifestations of intermittent muscle contractions causing repetitive, abnormal movements and/or postures with or without tremor [1], but also comprises numerous non-motor features (particularly anxiety and depression), reflecting shared pathophysiologic dysfunction in cortico-limbic-striatal circuits[2,3]. Despite treatment with medication and/or botulinum toxin injections, many persons with dystonia continue to experience symptoms resulting in physical disability, impaired quality of life and significant healthcare burden[4].

Stereotactic lesioning, though reasonably effective in controlling medically-refractory dystonic symptoms[5,6], has now largely been superseded by deep brain stimulation (DBS). Indeed, DBS has revolutionized the treatment of dystonia, and numerous randomized controlled trials have proven pallidal DBS to be an effective and relatively safe treatment option in a variety of dystonic syndromes[7–11]. Other regions, including the subthalamic nucleus (STN) and various thalamic nuclei (particularly in dystonic tremor or dystonic cerebral palsy) have also been successfully targeted[12–17].

Since DBS has become a mainstream treatment for dystonia, there is an increasing onus on movement disorder specialists to familiarize themselves with the planning and programming of neuromodulatory therapies and to have a clear and practical approach to troubleshooting problems in those with implanted DBS systems. However, despite increasing numbers of patients undergoing DBS for dystonia, there remains a dearth of knowledge regarding how best to manage individual patients in given clinical scenarios. Though some authors have attempted to standardize approaches [18,19], DBS programming in dystonia is largely driven by personal experience and local practice.

Certain characteristics of this cohort make it particularly challenging to manage. These include:

1. In contrast to patients with essential tremor (ET) and Parkinson's disease (PD), the effects of DBS on dystonia are not necessarily seen acutely. Weeks

or even months may be needed to assess the full impact of stimulation changes[20]. As such, programming cannot be reliably guided by real-time changes in clinical features, but often relies on the selection of the ‘likely’ best programming option.

2. As compared with other indications for DBS, dystonia is a highly heterogeneous clinical syndrome. Likelihood of response to DBS is influenced by a number of variables, including clinical phenotype, genetic factors and the presence or absence of structural brain abnormalities (figures 1 and 2)[21,22]. Creating unifying programming algorithms for such pathophysiologically diverse syndromes is understandably difficult. Additionally, whether specific clinical phenotypes or genotypes would benefit from individualised stimulation paradigms has not been evaluated in prospective, controlled studies.
3. Pallidal volumes vary markedly and can be very small in a proportion of patients with dystonia (especially those prone to poor outcomes), potentially making accurate targeting more challenging and limiting stimulation volumes in the target structure [23].
4. The experience with DBS in dystonia is less than for some other conditions such as PD.

In this review, we aim to provide clinicians with a practical, systematic guide for troubleshooting common issues encountered in people with dystonia treated with DBS, particularly suboptimal efficacy and stimulation-related side effects (figure 3 and 4). Given that the pallidum has the most evidence and is the preferred target for dystonia in most centres, our discussion focuses primarily on this. However, the principles of the suggested step-wise approach can be equally applied to other target nuclei. This narrative review is based upon the available literature, supplemented where appropriate by the authors’ personal experience.

SUB-OPTIMAL BENEFIT

Sub-optimal improvement following DBS for dystonia is not uncommon. Even in carefully selected populations deemed ‘ideal’ candidates, non-responder rates of up to 25% have been reported [7,24,25]. Reasons behind such treatment failures are often unclear, meaning that an uncomfortable degree of uncertainty can accompany DBS procedures for dystonia, despite optimal case selection. Physicians should develop a thorough, step-wise approach to troubleshooting this clinical problem (figure 3), working through patient, hardware and stimulation-related possibilities underlying suboptimal improvement, and modifying these where possible.

Patient assessment

Patient factors determining motor outcomes- what to expect

As alluded to previously, dystonia is a highly heterogeneous clinical syndrome with aetiologic underpinnings ranging from intrauterine and perinatal insults, through to hereditary genetic and metabolic disorders and acquired adult structural brain injuries. The response to DBS is not uniform across these entities and arguably the most important factor in achieving good outcomes is careful patient selection. A frank discussion of the range of possible outcomes, including which symptoms are likely to improve and which not, timelines for improvement, and potential adverse events is essential for patients to provide informed consent and to ground their expectations.

Numerous factors influence dystonia outcomes following DBS [21,25–29]. These include:

- **Clinical phenotype:** limb and axial dystonic movements benefit most from pallidal DBS, especially if part of isolated generalized, cervical or segmental dystonias. Conversely, there may be minimal benefit on speech or swallowing[7,9]. Isolated dystonia generally responds better than combined dystonia; important exceptions being myoclonus-dystonia and tardive syndromes[21,26,28,30]. Structural, hereditary degenerative or metabolic brain disease is generally a predictor of poor outcome[28].

- Nature of the dystonic movements: phasic contractions generally respond better than tonic spasms; fixed skeletal deformities, which may develop secondary to long-term abnormal posturing, do not generally improve with DBS[29,31].
- Disease duration and age at DBS surgery: young age and shorter disease duration at the time of surgery may portend better response in those with primary generalized dystonia[32,33].
- Genetic factors: within distinct isolated and combined dystonia syndromes, one's genotype majorly influences outcomes post DBS. For example, in isolated generalized dystonia cohorts, patients with DYT-*TOR1A* may respond better than those with DYT-*THAP1*, or those without a known genetic cause[34–37]. Similarly, in combined dystonia/parkinsonism syndromes, *TAF1* mutation carriers often show significant benefit following pallidal DBS, whereas those with *ATP1A3* mutations respond poorly, if at all[38,39].

Evaluation of motor outcomes following DBS must therefore always be judged in the context of the individual patient and their syndrome, and benchmarks for defining 'sub-optimal' response adjusted accordingly(Figure 1 and 2). For instance, a 40% improvement in dystonia motor scores for a patient with DYT-*TOR1A* might be unexpectedly low, whereas a similar improvement would be considered excellent in a patient with DYT-*PANK2*. Equally, patients who fail to respond as well as predicted should have their original diagnosis carefully re-considered(figure 3). Indeed, misdiagnosis -for example of combined dystonia syndromes as isolated dystonia, or of functional dystonia as organic disease- is one of the commonest reasons for unexpectedly poor responses [31].

Objective measurements – is there true worsening?

Improvements in dystonia motor state following DBS may evolve slowly over several weeks or months, and may not always be evident to patients, leading to mis-perception and therefore mis-reporting of their clinical course. It is therefore important, wherever possible, to objectively document changes in dystonia over time in order to unquestionably chart the patient's trajectory.

Most studies employ the Burke-Fahn-Marsden dystonia rating scale[40] for assessing generalized and segmental dystonia, while the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)[41] is commonly employed to rate cervical dystonia (CD). Numerous other specific rating scales for symptoms such as tremor (Fahn Tolosa Marin rating scale), blepharospasm, tardive involuntary movements and myoclonus exist[42] and are available on the International Parkinson and Movement Disorder website at www.movementdisorders.org. Dystonia severity should be scored (and preferably a video recording of the clinical examination performed) prior to DBS implantation, and re-scored periodically postoperatively. Such assessment tools usually comprise both motor and disability evaluations and allow objective quantification of new or persisting symptoms.

Currently employed clinical assessment tools are however imperfect. They are time-consuming to administer, require specific training, may be insensitive to mild disability or small changes, may only be available in a restricted number of languages, and may incorporate weighting systems which under-value certain bodily regions[43]. For some syndromes e.g. isolated truncal dystonia, no specific rating scales exist. Further, fluctuations in dystonia severity over time combined with operator-dependent subjectivity in the administration of rating scales make these single time-point assessments suboptimal. In the future, integrating technological advances such as 3D motion tracking and other kinematic measures, surface EMG and novel wearable technologies and into our clinical assessments may enhance our ability to identify and measure improvements in dystonia motor features [44–47]. These may even out-perform manual clinical rating scales[47].

Non-motor symptoms – important alternative explanations to consider

Non-motor symptoms- particularly sleep disorders, depression and anxiety including obsessive-compulsive disorder and social phobia-are highly prevalent in dystonic conditions[2,48]. They often pre-date motor manifestations, fail to correlate with dystonia severity (suggesting that they are an intrinsic feature of the disease process rather than a reaction to its physical manifestations) and do not necessarily improve in line with motor features[2]. Non-motor symptoms of dystonia may be a major source of distress, impaired quality of life and can be perceived by the patient as lack of DBS efficacy. These disease features should be systematically sought in patients reporting suboptimal efficacy because in contrast to motor features, they do not necessarily improve following DBS, but rather require tailored pharmacologic and non-pharmacologic treatment strategies[49–51].

Hardware Assessment

The pallidal target

The globus pallidus internus (GPi) is the major output structure of the basal ganglia, projecting particularly to the thalamus and midbrain for control of (primarily) contralateral limb movement[52]. It is comprised of an anteromedial portion subserving limbic functions within reward circuits, and a posterolateral sensorimotor area, the inferior (ventral) portion of which is generally considered the ‘sweet spot’ for maximal anti-dystonic effect, and the primary target for DBS in dystonia (figure 5)[53–55].

Microelectrode recordings in both humans and non-human primates have suggested a somatotopic organization of the GPi [52,56,57]. This can be conceived as an inverted homunculus within the GPi, with orofacial regions represented caudally, leg regions dorsally, and the upper limbs and trunk in between[52,57]. However, the relevance of these findings to DBS programming are uncertain, especially given that they are based on uni-cellular recordings which are fundamentally different from

macrostimulation[58]. Vayssiere et al. in a retrospective review of 19 patients with generalized dystonia identified significant correlations between active contact location and the body part exhibiting the greatest improvement, but only in the right pallidum. They speculated that this might reflect a more sophisticated, non-somatotopic organization of the dominant left pallidum (in most people)[58]. To-date, no studies have convincingly demonstrated regional-specificity of pallidal stimulation as being beneficial for specific body-region involvement in dystonia.

Targeting the GPi for dystonia-is the lead in the correct position?

DBS electrode placement in the GPi can be performed either with the guidance of microelectrode recordings (awake with light sedation), asleep with radiological confirmation, or with a combined approach. Both techniques are associated with their own risks and benefits. Microelectrode recordings offer the advantage of real-time interrogation of specific neuronal populations' burst frequencies and characteristics in an attempt to optimise lead placement within the target nucleus. It is however highly dependent on a surrogate marker of lead location, operator experience and may increase the risk of intracranial haemorrhage[59]. 'Awake' procedures are mainly focused on avoiding adverse events rather than observing improvements in clinical symptoms and are therefore of limited additional value in dystonia where symptomatic improvement is often delayed. Further, 'awake' DBS is often not an option for young patients, children or patients with intellectual disability or severe hyperkinetic movements. For these reasons, many centres now opt for asleep, image-verified lead placement. When using this approach, the importance of selecting an MR sequence that provides maximum contrast between pallidum and surrounding structures cannot be over emphasized. Optimal images will reveal the presence of an internal accessory lamina within the GPi (that should not be confused with the internal lamina separating GPe and GPi) as well as inter-individual variations in brain size and shape. Patients with secondary dystonia may have significant structural pallidal abnormalities-this may favour a different anatomical target such as the ventral oral anterior (Voa) nucleus of the thalamus or subthalamic nucleus (STN).

Accuracy of lead placement is an important determinant of outcomes following DBS. This can vary depending on operator experience, the preferred technique for target localization and intraoperative brain shift[60–62]. Some publications have suggested that lead mis-placement may represent the most common reason for poor DBS response in dystonia [31,63,64]. However, others found that pallidal volume of tissue activated was not significantly different between responders and non-responders, arguing that in a least a subset of individuals, endo-phenotype rather than accurate lead placement determines response to DBS[65]. Nevertheless, it is clear that without accurate lead placement, no amount of tinkering with stimulation parameters is likely to provide significant improvement. Assessment of lead position should therefore be one of the first steps in troubleshooting issues related to stimulation efficacy or development of side-effects [66]. Clinical features that may suggest sub-optimal lead placement include capsular and visual side effects (see below). However, not all sub-optimally placed leads will produce side effects at therapeutic stimulation parameters. DBS centers are increasingly moving towards image-verified approaches, where lead location on stereotactic MRI or stereotactic CT is part of routine data gathering during lead placement. This accurate assessment of lead location should allow identification of suboptimal lead placement. However, if these images are not available or if there are concerns about lead migration (an exceedingly rare complication in most centers), there may be a need to reassess lead location. This is best performed by obtaining an MRI sequence that demonstrates both the lead artefact and the anatomical target (for example, a proton density weighted sequence when visualizing the pallidum). Care must be taken to ensure MR conditionality of the implanted system, that impedances are within the normal range and that expertise is at hand should there be any hardware malfunction. Alternatively, if a suitable pre-operative MRI is available, an up-to-date CT scan can be co-registered with this using commercially available software to provide an estimate of lead location. However, one should always keep in mind that image registration errors may interfere with the veracity of such estimations.

In some cases of sub-optimal lead placement, repositioning may be necessary, though this does not guarantee later success[31,66]. There are no hard and fast rules about

when lead repositioning should be considered. In general however, deviations >2 mm from the intended target will significantly impair treatment efficacy[66,67], or will require the use of such high energy of stimulation to reach the target area that stimulation-related adverse effects become intolerable. Alongside lead position, many other factors will influence the decision for revision or placement of additional DBS leads. These include patient preference and expectations, comorbidities, residual symptom severity and the availability (or not) of directional steering systems, which theoretically may allow targeted current orientation towards the posteroventral pallidum and away from side-effect producing areas. However, the superiority of directional leads in this situation, remains to be proven.

DBS lead, extension cables and Implantable Pulse Generator (IPG)-are they working properly?

Therapy impedances and IPG function should be assessed at each visit, and are essential steps in the evaluation of patients with suboptimal therapeutic benefit or loss of efficacy. Abnormal impedances imply either an open circuit (high impedances) or short circuit (low impedances)[68]. Both of these can manifest as deterioration in symptom control, either acutely or sub-acutely (sometimes mimicking progression in the underlying disorder), or as a shocking sensation [69,70].

Short circuits can result from infiltration of body fluids into connections, or lead/cable fractures[68]. Open circuits can also result from lead/cable fractures, or sometimes damage to adaptors used during transition from older to newer systems. In our experience, macroscopic fractures generally occur in the setting of direct trauma (however, they can also occur when no such history is present), and can sometimes be identified on palpation, or using X-ray or CT evaluation[68]. Some have reported that hardware-related complications (particularly lead/cable fracture and migration) are over-represented in the dystonia population-up to double that of other indications such as ET or PD- although that is not our experience[69,70]. Numerous factors could account for this. The craniocervical musculature is frequently involved in both

generalized, segmental and focal dystonias, which likely places additional traction stress on DBS extension cables. Moreover, in contrast to most other movement disorders, the therapeutic effect of DBS in dystonia can take weeks to establish-DBS hardware is therefore exposed to sheer/stress forces for a longer period of time after implantation.

Approaches to management of impedance problems largely depend on whether abnormal impedances affect single or multiple contacts, whether these contacts are being used, the association with changes in clinical state and whether, through alternate programming approaches, sufficient therapeutic benefit can be maintained without inducing side effects. In the absence of changes in efficacy or side-effect profiles, abnormal impedance measurements do not necessarily require intervention. Importantly however, it may limit MR conditionality. Loss of clinical efficacy or side effects associated with abnormal therapeutic impedances to a single contact should first be addressed by attempts at re-programming using alternative (often adjacent) usable contacts. If this fails, intraoperative testing to localize the problem may be necessary, and failing this, sequential replacement of potentially defective components, starting with the IPG but then working upwards, sometimes requiring replacement of the entire system[68].

In contrast to the sub-acute decline or shocking sensations experienced with DBS lead and extension cable faults, IPG malfunction often manifests acutely with unexplained switching off of the system and subsequent acute clinical deterioration. Such abrupt loss of therapeutic efficacy can be particularly dangerous, due to the precipitation of status dystonicus; IPG replacement in this setting is a surgical emergency[71,72]. Thankfully, such events are rare with modern IPGs. Reasons for these differences in clinical presentation may include the fact that lead malfunctions usually occur unilaterally, and may thus be mitigated by continued therapeutic efficacy on the other side as well as continued (albeit suboptimal) stimulation of the target nucleus on the affected side[69].

Stimulation Assessment

Initial Programming-identifying the 'best' contact

Initial programming of DBS in dystonia begins with monopolar screening of all contacts on the DBS electrode. Stimulation intensity is progressively increased at each level in 0.5mA/V increments, with frequency and pulse width set around 130Hz and 60-90 μ s, respectively[19]. If directional steering systems are employed, the screening process should, in the first instance, be performed using classic 'ring-mode' stimulation. The optimal time to perform monopolar screening is debated. In ET and PD in particular, postoperative 'lesion effect' as a result of electrode insertion may transiently improve symptoms and obfuscate clear assessments[20]. This effect tends to be less prominent in dystonia however, and we generally perform initial screening 1-2 days after implantation.

Screening serves two purposes. First, it allows the physician to establish the upper limit of the therapeutic window, in particular, the stimulation intensity at which side-effects appear at each contact location. Second, though changes in dystonia are not consistently observed during the screening evaluation, phasic dystonic features may vary with stimulation, giving a clue to the potential 'best contact' for optimal anti-dystonic effect[73]. Both improvement and worsening of dystonic symptoms with stimulation at a particular contact may predict future therapeutic efficacy[74], as may the appearance of dysarthria[74].

If changes in clinical state are observed during the monopolar screening, the contact chosen for initial stimulation should be the one with the best benefit: side-effect profile. If the monopolar review does not suggest a 'best' contact, our practice is to begin stimulation on a single, more ventral contact bilaterally. Thereafter, stimulation intensity can either be increased gradually, until optimal anti-dystonic effect is observed ('bottom-up' approach), or set at 0.5-1mA/V below the threshold for side-effects, with later down-titration in order to preserve battery life ('top-down approach'). Most studies employing pulse width and frequency settings similar to those above find optimal dystonia improvements in the region of 3.0-

3.5mA/V[7,9,24,32,33,72,75–77], and therefore, if using the ‘bottom-up’ approach, we recommend starting amplitudes of 2.0-2.5mA/V. After initial programming, the patient should be reviewed between 6 weeks and 3 months later for further adjustments[7,8]. Unless significant asymmetry in dystonic symptoms exist, we generally begin with similar stimulation intensities in both GPi. Unilateral increases in pallidal stimulation can be used to target contralateral limb dystonic symptoms, while bilateral increases in stimulation intensity are generally employed for craniocervical, generalized and axial dystonic symptoms. The majority of patients obtain substantial improvements within the first 3-4 post-operative months.

‘Advanced’ programming approaches

Most patients will obtain sufficient benefit following initial ‘simple’ programming. However, there exists significant variability in outcomes following DBS for dystonia[8,25]. Once other contributing factors- inaccuracy in lead placement, hardware issues, misdiagnoses of the clinical syndrome, fixed deformities etc. –have been explored, a number of more advanced programming approaches may help to maximize clinical benefit[31]. Many of these strategies have not been evaluated in a controlled trial setting and are therefore intended as a practical guide rather than as rigid framework.

Stimulation Amplitude

Increasing stimulation amplitude has consistently been associated with improved dystonia outcomes and is generally the first step when attempting to maximise clinical benefit[78]. We usually review patients on a 3-6 monthly basis, up-titrating stimulation, if necessary, in 0.1-0.5mA/V increments, while ensuring that the final stimulation parameters remain below those for side effects. Patients can also modify their stimulation at home using their patient programmers. In this instance, we generally suggest 0.1mA/V increments, and remind them to allow at least 2-3 weeks

following any alterations for clinical effects to emerge; not doing so risks unnecessary over-stimulation. If patients are given the option of trying multiple programs using their controller, they should retain the option of returning to their original settings, in case they develop intolerable side-effects in a delayed fashion. Progressive improvement in dystonia following stimulation adjustments may continue beyond 6 months, particularly for tonic components[7,24].

Previous notions about balancing effective anti-dystonic stimulation with trying to preserve battery life [79] are becoming less of a consideration with the increasing use of rechargeable systems, and within the limits of side-effect induction, stimulation should be adjusted to achieve optimal dystonia control. Whether this approach has implications on the possible development of tolerance remains unknown.

Alternative/multiple contact selection

Sub-optimal benefit from adequate stimulation (generally $>4\text{-}5\text{mA/V}$ or limited by side-effects) using the 'best' contact chosen during monopolar review should lead to a trial of other DBS electrode contacts. Which contacts to use as a second choice can be guided by the initial monopolar screening findings, a further monopolar review or review of lead placement on postoperative imaging. If this is unhelpful, we suggest proceeding sequentially from the most ventral to the more dorsal contacts. More recently, software packages allowing patient-specific reconstruction of lead position, target nucleus and adjacent structures on the basis of postoperative brain imaging have been developed. Many of these allow modelling within this space of the volume of stimulated tissue for a given set of stimulation parameters. The limitations of this approach must be acknowledged, including errors in co-registration of lead placement within the anatomical models, assumptions used for current spread and threshold activation levels. Nevertheless, due to the frequent temporal disconnect between stimulation changes and clinical benefit, this may be particularly valuable for DBS programming in dystonia, although they remain unproven.

Aside from changing the active contact in monopolar configuration, another commonly employed option is the use of double monopolar stimulation (2, generally adjacent negative contacts on the DBS electrode) in an attempt to increase the volume

of tissue stimulated. In our experience, focusing on the deepest contacts in the posteroventral pallidum appears to provide most benefit.

Frequency

Most studies to date have employed medium-range frequencies (130-185Hz) in their initial programming for both focal and generalized dystonia syndromes, and this is also our practice[9–11,34,55,75,80,81]. Moro et al. evaluated the acute effects of altering stimulation parameters in 8 patients with CD, and found significant benefit to increasing frequency, greatest at 130Hz[78]. Others have similarly concluded that the optimal stimulation frequency for dystonia lies in the higher range of 130-250Hz[82]. In a trial of 14 patients with CD initially programmed with a low-frequency stimulation setting (70Hz), most required increases in frequency to maintain clinical benefit[83], while other trials of low frequency stimulation showed similarly high rates of switching to high-frequency settings[84]. Moreover, if the STN is used as a target for dystonia, high-frequency stimulation appears superior[85].

Some groups have however suggested that lower frequency (60-80Hz) pallidal stimulation can be used without compromising therapeutic efficacy, albeit generally with higher PW (>200µs)[86]. Importantly, low frequency stimulation may minimize side-effects (see below), enabling more ventral pallidal stimulation[87].

Pulse width (PW)

A variety of different pulse-width settings have been employed in various studies on DBS in dystonia, though few have specifically examined the effect of variations in PW on clinical efficacy. Though some groups preferentially employ long pulse-widths (450µs) with relatively lower stimulation amplitudes[34,88,89], studies comparing the use of short (60–90 µs), medium (120–150 µs) or long (450 µs) PWs in

terms of anti-dystonic efficacy in focal or generalised dystonia have generally found no differences[11,34,75,78,90]. Though follow-up times in many of these studies were relatively short (often hours/days, whereas anti-dystonic effects may take weeks to establish), they provide a reasonable rationale for the use of short pulse-width programming of DBS for dystonia, certainly in the initial stages. Use of lower PW not only limits battery drain, but is thought to increase the therapeutic window at given stimulation intensities[86,90]. Newer devices enable stimulation at PW as low as 10 μ s, though use of such stimulation parameters has not been rigorously evaluated in the dystonia population.

Interleaving stimulation

Interleaving stimulation refers to a programming paradigm whereby two different stimulation programs are interleaved on two contacts on the same electrode at identical stimulation frequencies, alternating which is switched ON and OFF up to 125 x per second. The voltage/current and pulse width delivered to each contact can be individually adjusted, allowing for more nuanced, region-specific stimulation. This option is generally employed either to mitigate stimulation side-effects or in an attempt to improve therapeutic efficacy. The evidence surrounding its efficacy is limited, and it is often used once trials of monopolar, double monopolar and other approaches to programming have failed[91–93]. That being said, some groups have noted improvements using this approach in patients with suboptimal outcomes using other programming methods[91,94]. Interleaving is generally instituted between the best and ‘second-best’ contacts[91]. The major drawback is accelerated battery drain.

Other options

In patients with adequately sited leads, in whom all stimulation options have been exhausted without significant improvement, a small number of other therapeutic options remain. These include the introduction (or reintroduction) of anti-dystonic

medications (e.g. anticholinergics, benzodiazepines), the addition of botulinum toxin injections, especially for focal symptoms or indeed additional lead placement, either targeting non-stimulated areas within the pallidum or another anatomical target. Cif et al. demonstrated that placement of a second pallidal DBS lead can produce further improvement in patients with generalized dystonia, especially if they had shown initial benefit with ‘secondary’ worsening[95]. Implanting a second lead in a different nucleus within the dystonia network, such as the STN or ventral oral (Vo) thalamus is another option. A small number of trials have demonstrated efficacy of the STN target in dystonia[96]. Although one trial suggested a trend to improved outcomes in the STN groups compared to GPi, a suboptimal location of pallidal leads in enrolled patients was suggested [97,98]. Further head-to-head studies are needed to define if there exists a specific dystonia population in whom preferential stimulation of this nucleus should be considered. In some secondary dystonias, particularly those secondary to inherited metabolic diseases, destructive pallidal lesions necessitate consideration of alternative targets, such as the Vo thalamus, STN, pallidothalamic tract (PTT) or even the cerebellum[99–101].

The decision process regarding replacement or re-positioning of DBS leads in dystonia is an individualized process which must take into account numerous factors including:

- Current lead position and benefit: If an optimally sited lead has never led to clinical benefit, additional lead placement in this same nucleus may not provide benefit. However, if there was significant benefit which was not sustained, an additional lead placement could be considered[89].
- Expected outcomes: These are dependent on multiple factors, as detailed above. Again, in cases of treatment failure, the accuracy of the original diagnosis should always be re-considered.
- Surgical risk
- Patient preference

Long-term efficacy

There is a general consensus in the literature as well as a wealth of observational data suggesting that deep brain stimulation is an effective long-term management strategy for dystonia. Numerous publications have documented sustained benefit for well over a decade following the procedure[24,102–104], and as such, persistent treatment efficacy is to be expected. That being said, some patients require increases in stimulation parameters over time in order to maintain benefit and it is increasingly recognized that some patients experience secondary deteriorations after initial improvements and plateau in dystonic symptoms[105–107].

SIDE- EFFECTS

Aside from sub-optimal efficacy, side-effects are the other principal reason requiring troubleshooting of DBS systems for dystonia. Side-effects may emerge as an intrinsic complication of stimulation (and in these cases may limit escalation of therapy), as a result of suboptimal lead placement e.g. too close to the internal capsule, producing capsular side-effects, or as a combination of the two. Below, we review the more common side-effects associated with pallidal stimulation and suggested approaches to managing these while allowing continued therapeutic benefit.

Parkinsonism

Stimulation-related parkinsonism is one of the most commonly encountered side effects of pallidal stimulation. It generally manifests with bradykinesia, gait disturbance (festination, freezing) and/or micrographia, and can be so severe as to mimic neurodegenerative parkinsonism, though in contrast, dopamine transporter imaging is usually normal and the condition is at least partially reversible upon stopping stimulation[108,109].

The pathophysiologic underpinnings of this phenomenon remain uncertain, but it appears to relate to altered pallidal connectivity rather than current spread to adjacent structures such as the internal capsule[109]. It has been suggested that altered pallidal outflow to thalamo-cortical areas or the pedunculopontine nucleus (particularly for gait disturbances) may be involved, though further evaluation of such network alterations is required[110,111].

Management of stimulation-related parkinsonism can be challenging, as it is generally encountered with postero-ventral GPi stimulation, which is also the region most likely to produce anti-dystonic effects. Options include moving to a more dorsal stimulation contact (dorsal pallidal stimulation often significantly improves parkinsonian signs), or reducing stimulation amplitude or frequency (<100Hz)[18], though often a balance needs to be struck between sufficiently improving dystonic features while minimizing parkinsonism.

Speech Impairment

Speech abnormalities are the other common stimulation-related adverse effects of pallidal stimulation. They affect 10-30% of this population[7,24], and generally manifest as either hypophonic dysarthria (low volume, indistinctly articulated and fast rate-similar to parkinsonian speech) or stuttering, effortful speech[112–114]. Medial and posterior pallidal stimulation appears to be a risk factor for dysfluency, possibly due to current spread to capsular fibres, or to interference with pallidal output[113,114]. Options for mitigation include reducing stimulation amplitude, moving to a more lateral contact (either in monopolar, double monopolar or bipolar organization) or if directional leads are implanted, steering current laterally, away from the internal capsule. It is important to note however that if speech impairments are dystonia-related, patients may well improve following DBS [113].

Capsular effects

The internal capsule forms the medial border of the GPi. As such, it can be affected by current spread outside of the theoretical anti-dystonic sweet spot in the postero-lateral-ventral GPi. Manifesting as tonic contractions of the contralateral face, arm or

leg, this adverse event is more likely encountered with medially-placed electrodes or when using high stimulation parameters. Aside from reducing stimulation intensity, mitigation strategies may include use of bipolar stimulation (1 negative contact adjacent to 1 positive contact on the same electrode) or if available, directional current steering. Bipolar stimulation creates a more focused field, maximal near the cathode, and is useful if side-effects are the result of excessive radial spread of current to adjacent structures in monopolar mode[19].

Phosphenes

The appearance of phosphenes signifies current spread medially and inferiorly from the anti-dystonic ‘sweet spot’ in the posteroventral GPi to the optic tract[7], and is more commonly encountered if employing a coronally oblique trajectory to the GPi. In our practice, the coronal angle of approach is roughly parallel to the falx, such that the deepest contacts lie superior and lateral to the optic tract, and phosphenes are rarely observed. Their appearance at low threshold usually suggests that the stimulated contact is located ventro-medially in the pallidum. Our practice in such instances is to use a more dorsal contact, which we find often produces better anti-dystonic effects; notably, phosphenes does not necessarily correlate with long-term clinical efficacy[74]. Reducing stimulation intensity, or changing to bipolar stimulation mode may also reduce the volume of stimulated tissue and improve the issue.

Other side-effects

Aside from those mentioned above, pallidal stimulation rarely produces other side-effects. Neuropsychiatric and cognitive disturbances can occasionally occur post-operatively, but are rarely directly attributable to a stimulation effect[115]. Modulation of the more ‘limbic’ ventral pallidal region may explain these phenomenon[116]. Scattered reports of intracranial malignancy in patients with pallidal DBS have also surfaced, though their attribution to anything other than mere chance would be premature[117,118].

Conclusion

The increasing uptake of DBS in movement disorders mandates that clinicians be comfortable with its use in a multitude of clinical settings. In contrast to PD and ET however, where well-established algorithms provide clear guidance regarding programming and troubleshooting of adverse events, the complexity of dystonia syndromes has meant that for this disorder, similar recommendations have been difficult to devise. Nevertheless, increasing numbers of patients are receiving DBS for dystonia. A significant number these will experience problems either relating to suboptimal efficacy or side-effects. It is therefore critical that movement disorder physicians have a framework for approaching such issues (figures 3 and 4). Herein, we provide such a pragmatic, clinically-focused guide based on our experienced and a critical appraisal of the literature, in the hope of improving the care for patients with dystonia treated with DBS.

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All procedures followed were in line with the journal's ethics policy

Authors' contributions:

1A, conception and design of the study; 1B: acquisition of data; 1C, analysis and interpretation of data.

2A, drafting the article; 2B, revising it critically for important intellectual content
3, Final approval of the version to be submitted.

EM 1A, 1B, 1C, 2A, 3

NV 1A, 1C, 2B, 3

ADR 1A, 1C, 2B, 3

KPB 1A, 1C, 2B, 3

LZ 1A, 1C, 2B, 3

TF 1A, 1C, 2B, 3

PL 1A, 1C, 2B, 3

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