ADVANCED MANAGEMENT OF PD, ET AND DYSTONIA AND TROUBLESHOOTING

Joohi Jimenez-Shahed, MD
Baylor College of Medicine
Houston, TX

Introduction
Although the efficacy of deep brain stimulation (DBS) for treatment of patients with movement disorders depends on many interrelated factors, a major determinant is appropriate programming of the DBS device. After optimal lead placement, the first step is to focus the field of stimulation on the desired anatomic subregion of the target nucleus. The stimulation field is shaped in different ways, including selection of the appropriate stimulating contact(s), and titrating the amplitude, pulse width and/or frequency of stimulation. The main areas of interest are the dorsolateral subthalamic nucleus (STN), the posteroventral region of the globus pallidus interna (GPi), and the ventral intermediate (ViM) nucleus of the thalamus. If the field of stimulation spreads outside of these areas of interest, unwanted side effects may occur, which can limit both the efficacy of DBS therapy as well as patient satisfaction. Given the often progressive nature of symptoms, the need for stimulation titration must be balanced with the risk of causing stimulation side effects, and the practitioner should be able to ascribe new symptoms to disease progression versus stimulation, though some may be delayed in onset. Apart from field shaping, strategies for managing stimulation-induced side effects may include use of interleaved stimulation, current steering, or activation of patient control and group settings.

Advanced management of Parkinson's disease (PD)
The main effects of DBS therapy in PD are to reduce or eliminate motor fluctuations, dyskinesias, or refractory tremor. A general principle is that symptoms that improve with levodopa during the pre-operative phase tend to improve post-operatively with stimulation in place, with additional control of treatment complications. Long-term follow-up studies demonstrate that with appropriate programming and medication management, major features such as tremor, rigidity and dyskinesias remain significantly improved following both STN and GPi DBS. However, other features may emerge, including cognitive decline, mood disorders, impulse control disorders, speech difficulties, gait/balance difficulties, or sleep problems. The challenge for the practitioner at each follow-up visit is determining whether a patient's complaints warrant stimulator adjustment (and if so, whether higher or lower) or medication adjustment (and if so, whether higher or lower doses, or new medications are needed).

- **Worsening or recurrent dyskinesia –** a general guideline is that STN stimulation may worsen dyskinesias and therefore requires greater medication reduction, while GPi stimulation can attenuate dyskinesia without need for medication reduction.
    - In patients treated with STN DBS, worsening dyskinesias in the early post-operative phase can be dealt with by reducing medications. If this leads to intolerable side effects, then reducing the stimulation field (lowering amplitude or bipolar or interleaved stimulation when available) may also be considered. More chronically, worsening dyskinesias may improve with either stimulation titration (either direction) or medication reduction. Patient control parameters may allow for safe ad lib adjustment within defined parameters. Although dyskinesia induction often indicates good electrode placement and corresponding motor benefit, in some patients, STN DBS induces severe dyskinesias independent of medication effect ("runaway dyskinesias"), which poses a different management challenge. In such cases the following strategies can be considered: activating dorsal contacts within the zona incerta, lowering the frequency of stimulation, or rescue lead placement into the GPi.
    - Uncommonly, dyskinesias may worsen in individuals treated with GPi DBS. This may result from unintended activation of the globus pallidus externa (GPe), and may improve by moving the stimulation field more rostrally, or by medication reduction.
- **Worsening speech** – Speech impairment in PD is described as a hypokinetic dysarthria, but may have many features. In a series of STN-DBS, speech disorders were worse than in non-DBS patients, and all tended to improve with stimulation OFF. The most robust improvements were seen in individuals with strained or spastic dysarthria types, compared to those with stuttering or breathy voice types, and is most likely due to spread of current laterally to corticobulbar fibers. Practitioners should first determine if speech improves with stimulation off (one side, the other side, or bilateral). In cases of appreciable improvement, the following strategies can be tried: reducing stimulation field (lower amplitude, or bipolar

or interleaved stimulation when available), reducing stimulation frequency or pulse width, activating patient control parameters, or speech therapy. Stimulation-induced speech disorders are less commonly reported in GPi DBS, but similar management strategies may be tried. New electrodes with current steering capabilities may allow shifting the stimulation field away from the corticobulbar fibers.

- **Worsening gait** – Symptoms may include worsened balance, shuffling, festination or freezing of gait. Individuals with on-period freezing prior to DBS are likely to continue experiencing this symptom after DBS. Gait worsening after DBS is otherwise likely due to a complex interaction between the progression of the disease, effects of stimulation, reduction in postoperative medication dosage, aging processes, and co-morbidity. A close temporal association to stimulator activation or an adjustment suggests a stimulation-induced problem, although this association may not always be found. Management strategies include: increasing or decreasing medications, increasing or decreasing the field of stimulation, increasing or decreasing the intensity of stimulation (frequency or pulse width), or physical therapy. Some reports have suggested that unilateral adjustment may improve gait symptoms. Successful management of gait worsening using these measures is more commonly reported in PD patients treated with STN DBS, but has also been reported in small numbers in cases of GPi DBS, where, anecdotally, reducing the stimulation field or intensity can be helpful. Of note, this feature has been described in patients treated with GPi DBS for non-parkinsonian disorders (e.g., dystonia).
- **Non-motor symptom management –** In general, studies suggest improvement in many non-motor symptoms after STN DBS, once stimulation is optimized. Emergence of cognitive and psychiatric symptoms following DBS can be due to complex interplay between surgery, stimulation and medications. Acute development or worsening of cognitive and psychiatric symptoms are more likely related to stimulation spread to the associative and limbic areas of the STN, and is more likely to involve stimulation using inferior contacts. Symptoms may include euphoria, impulsivity and mania, and can be addressed with stimulation reduction. More long-term changes can be related to medication adjustment. Emergence of depression and apathy may relate to reduction in dopaminergic medications. Impulse control disorders have been reported to emerge, worsen, or improve after DBS and several methods may need to be tried to address this problem. The most consistent cognitive adverse effect of DBS surgery is reduction in verbal fluency, which is most likely attributable to surgical effects rather than stimulation or medication changes. There is limited comparative evidence regarding similar outcomes following GPi DBS for PD.

Advanced management of essential tremor (ET)

- **Emergence of speech issues –** Speech problems may occur in individuals with ET, or may emerge/worsen following ViM stimulation. They are more likely to occur with bilateral stimulation and may relate to stimulation spread to corticobulbar or cerebellothalamic pathways. The diagnostic algorithm should include assessment with the stimulator off (unilateral and bilateral), with the stimulation on at optimized settings, and with supra-therapeutic settings, in order to determine if it is stimulation induced. If so, management strategies may include reducing stimulation, using bipolar or interleaved configurations (when available), changing contacts, or activating patient control options to use variable settings during different daily activities. Current steering may have a role in avoiding this side effect, when segmented electrodes are used.
- **Emergence of gait issues –** Gait ataxia may be a feature of chronic, long-standing ET, but new or worsening gait problems may occur following ViM stimulation. Spread of stimulation to the internal capsule may produce a “stiffening” of gait (possibly accompanied by other capsular side effects) whereas stimulation of cerebellothalamic fibers may produce ataxia. Management strategies are similar for speech issues.
- **Loss of effect -** Loss of stimulation efficacy is established in long-term reports of DBS for ET, but precise mechanisms are unknown. Although ET can progress over time, experience suggests that a phenomenon called “tolerance” to stimulation may develop. This may take several forms, including tremor rebound (a temporary increase of tremor intensity over the pre-operative state occurring a few seconds after switching off DBS), habituation of tremor suppression (the loss of sustained tremor control over days to weeks after programming), and late therapy failure (loss of effect of stimulation following at least 1 year of satisfactory tremor suppression with DBS). Theories for development of tolerance include disease progression, inadequate electrode location, resolution of microthalamotomy effects, or adaptation of neural networks to localized chronic stimulation. No definitive management strategies exist, but these can include repeated re-programming, limiting stimulation frequency, turning stimulation off at night or stimulation holidays, switching between different stimulation parameters (group settings), electrode repositioning, or rescue lead placement.

Advanced management of dystonia

- **Suboptimal benefit –** This may result from disease related factors, electrode positioning, or programming factors. Pre-op factors may include disease phenotype (e.g., primary vs. secondary dystonias), age since onset of dystonia, or presence of contractures or other deformities limiting improvement in abnormal postures. Electrode positioning and localization of the active contact play an important role. Response of dystonic symptoms to stimulation is more often delayed compared to tremor or parkinsonian features. Re-programming may require titration of amplitude, pulse width or frequency, changing contacts, or adding a 2nd contact. Certain forms of dystonia (e.g., DYT-1) may respond best to 60Hz stimulation.
- **Stimulation-induced parkinsonism –** Stimulation-induced bradykinesia and gait disorders have been described, producing mild parkinsonism. It may be more likely to occur with stimulation of the ventral contacts. Reducing stimulation intensity or changing to a dorsal contact may be tried, but should be balanced with the potential for worsening dystonia.
- **STN stimulation –** STN stimulation has been proposed as an alternative to GPi stimulation in some cases of dystonia. In cervical dystonia patients, this may result in greater programming side effects including dyskinesias.

Troubleshooting

- **Managing therapy "failures" –** Reasons for perceived failure after DBS treatment may include a non-ideal initial DBS candidate, inadequate pre-operative evaluation, unreasonable expectations of outcome, hardware complications, suboptimal lead placement, suboptimal programming, disease progression, and tolerance/habituation. Diagnostic and management strategies should include a review of the pre-operative history and diagnosis (including comparison of pre-operative functioning to present functioning), checking hardware integrity, checking the programing strategy (i.e., repeating a monopolar review and taking note of stimulation-induced side effects), and checking lead placement.
- **When to revise an electrode –** Indications for revision may include lack of efficacy, side effects of stimulation, infection, lead migration, or lead damage. In cases of lack of clinical efficacy or side effects, it is important to carefully consider the electrode positioning.
- **Abnormal impedance values –** Interrogating the DBS device should be routinely performed at all clinic visits and before an IPG exchange to check hardware integrity. Clinical symptoms may or may not be present when a short or open circuit develops, but they should be noted and managed appropriately to avoid therapy failure or side effects.

References:

- Andrews C, Aviles-Olmos I, Hariz M, Foltynie T. Which patients with dystonia benefit from deep brain stimulation? A metaregression of individual patient outcomes. J Neurol Neurosurg Psychiatry. 2010;81:1383-9.
- Angeli A, Akram H, Zacharia A, Limousin P, Hariz M, Zrinzo L, Foltynie T. Varying time-course of effects of high frequency stimulation of sub-regions of the globus pallidus in patients with parkinson's disease. Parkinsonism Relat Disord. 2015;21:597-602.
- Baizabal Carvallo JF, Simpson R, Jankovic J. Diagnosis and treatment of complications related to deep brain stimulation hardware. Mov Disord 2011;26:1398-1406.
- Baizabal-Carvallo JF, Kagnoff MN, Jimenez-Shahed J, Fekete R, Jankovic J. The safety and efficacy of thalamic deep brain stimulation in essential tremor: 10 years and beyond. J Neurol Neurosurg Psychiatry. 2014;85:567-72.
- Castrioto A, Lhommée E, Moro E, Krack P. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. Lancet Neurol. 2014;13:287-305.
- Dafsari HS, Reddy P, Herchenbach C, Wawro S, Petry-Schmelzer JN, Visser-Vandewalle V, et al. Beneficial Effects of Bilateral Subthalamic Stimulation on Non-Motor Symptoms in arkinson's Disease. Brain Stimul. 2016;9:78-85.
- Ellis TM, Foote KD, Fernandez HH, Sudhyadhom A, Rodriguez RL, Zeilman P, Jacobson CE 4th, Okun MS. Reoperation for suboptimal outcomes after deep brain stimulation surgery. Neurosurgery. 2008;63:754-60.
- Falowski SM, Bakay RA. Revision Surgery of Deep Brain Stimulation Leads.Neuromodulation. 2016;19:443-50.
- Farris S, Giroux M. Retrospective review of factors leading to dissatisfaction with subthalamic nucleus deep brain stimulation during long-term management. Surg Neurol Int. 2013;4:69.

- Farris S, Vitek J, Giroux ML. Deep brain stimulation hardware complications: the role of electrode impedance and current measurements. Mov Disord. 2008;23:755-60.
- Kenney C, Simpson R, Hunter C, et al. Short-term and long-term safety of deep brain stimulation in the treatment of movement disorders. J Neurosurg 2007;106:621-5.
- Moro E, Lozano AM, Pollak P, Agid Y, Rehncrona S, Volkmann J, et al. Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. Mov Disord. 2010;25:578-86.
- Okun MS, Rodriguez RL, Foote KD, Sudhyadhom A, Bova F, Jacobson C, et al. A case-based review of troubleshooting deep brain stimulator issues in movement and neuropsychiatric disorders. Parkinsonism Relat Disord. 2008;14:532-8.
- Okun MS, Tagliati M, Pourfar M, Fernandez HH, Rodriguez RL, Alterman RL, Foote KD. Management of referred deep brain stimulation failures: a retrospective analysis from 2 movement disorders centers. Arch Neurol. 2005;62:1250-5.
- Patel N, Ondo W, Jimenez-Shahed J. Habituation and rebound to thalamic deep brain stimulation in long-term management of tremor associated with demyelinating neuropathy. Int J Neurosci. 2014;124:919-25.
- Picillo M, Lozano AM, Kou N, Munhoz RP, Fasano A. Programming Deep Brain Stimulation for Tremor and Dystonia: The Toronto Western Hospital Algorithms. Brain Stimul. 2016;9:438-52.
- Picillo M, Lozano AM, Kou N, Puppi Munhoz R, Fasano A. Programming Deep Brain Stimulation for Parkinson's Disease: The Toronto Western Hospital Algorithms. Brain Stimul. 2016;9:425-37.
- Pilitsis JG, Metman LV, Toleikis JR, et al. Factors involved in long-term efficacy of deep brain stimulation of the thalamus for essential tremor. J Neurosurg 2008;109:640–6.
- Pollo C, Kaelin-Lang A, Oertel MF, Stieglitz L, Taub E, Fuhr P, Lozano AM, Raabe A, Schüpbach M. Directional deep brain stimulation: an intraoperative double-blind pilot study. Brain. 2014;137:2015-26.
- Rolston JD, Englot DJ, Starr PA, Larson PS. An unexpectedly high rate of revisions and removals in deep brain stimulation surgery: Analysis of multiple databases. Parkinsonism Relat Disord. 2016;33:72-77.
- Tsuboi T, Watanabe H, Tanaka Y, Ohdake R, Yoneyama N, Hara K, et al. Distinct phenotypes of speech and voice disorders in Parkinson's disease after subthalamic nucleus deep brain stimulation. J Neurol Neurosurg Psychiatry. 2015;86(8):856-64.
- Volkmann J, Wolters A, Kupsch A, Müller J, Kühn AA, Schneider GH, et al. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. Lancet Neurol. 2012;11(12):1029-38.