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The Transition of Deep Brain Stimulation from Disease Specific to Symptom Specific Indications

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Abstract: The success of chronic deep brain stimulation (DBS) and electrical neuro-network modulation (ENM) to address neurological and neuropsychiatric disorders has led the Food and Drug Administration (FDA), and also other worldwide regulatory agencies to grant approval for the use of DBS in specific disorders. In the United States, DBS is FDA approved for the treatment of advanced Parkinson's disease (PD), essential tremor (ET), obsessive compulsive disorder (OCD), and for dystonia. OCD and dystonia have been approved under a mechanism referred to as a humanitarian device exemption (HDE). However, as the field of DBS and ENM evolve there has been a shift in practice patterns from targeting diseases to targeting specific and disabling symptoms. This shift has been driving interdisciplinary DBS boards to collect, and to address symptom profiles in all potential DBS candidates. Based on a specific symptom profile, a strategic and personalized medicine approach can be undertaken. The personalized approach will take into consideration the brain target, a unilateral versus a bilateral procedure, and the potential for use of more than one DBS lead per brain hemisphere. Additionally, a personalized approach to DBS will also facilitate improved pre-operative medication adjustments, as well as optimal post-operative medication, behavioral, and device management.

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Key words：DBS, Selection, Indications, Network, Complications

The advent of chronic deep brain stimulation (DBS) for the treatment of neurological and neuropsychiatric disorders[1)2)] led the American Food and Drug Administration (FDA), as well as other worldwide regulatory agencies, to grant approval for the use of DBS in specific neurological disorders. In the United States DBS is FDA approved for the treatment of advanced Parkinson's disease (PD) and for essential tremor (ET). DBS has also been approved under a mechanism called a humanitarian device exemption (HDE). This exemption can be used to treat select cases of dystonia and obsessive compulsive disorder[3)～5)], as long as institutions performing DBS surgery for these indications have an IRB approved protocol. As the field of DBS and electrical neuronetwork modulation continues to evolve, there has been a gradual shift in practice patterns from targeting specific diseases, to targeting specific and disabling symptoms[3)]. In this paper, I will discuss the shift in the DBS field toward a more symptom based approach.

A Shift in the Focus of DBS Screening Boards

Potential DBS patients typically present to experienced centers for comprehensive and expert interdisciplinary screening[6)7)]. This screening process typically involves a neurologist, a neurosurgeon, a neuropsychologist, a psychiatrist, a physical therapist, an occupational therapist, and a speech therapist. Following this interdisciplinary evaluation, the next step in most expert centers is a meeting of a DBS board which is made up of all the health professionals who have evaluated a specific patient. The board is charged with discussing the risk-benefit profile for each patient, and in strategizing the safest approach for an operation (unilateral vs. bilateral, specific brain target, pre-post operative monitoring). Some patients will be approved, some conditionally approved, and some denied DBS[3)6)]. Over the last decade there has been a gradual change in the content of the discussions taken up by these DBS boards. The question has shifted from "what disorder should we treat with DBS", to "what symptom(s) should we treat with DBS".

What Symptom(s) Should We Address with DBS

The most important question that we can ask a potential patient interested in receiving DBS therapy is what symp-

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tom or symptoms do they expect to be adequately addressed by DBS therapy. It is not uncommon for a patient, and for a treating DBS team to be "out of synch" on this issue. A patient may, for example, desire post-DBS speech and gait improvement, while in contrast the treating team may be highly focused on issues such as on-off fluctuations and dyskinesia[8]. Each FDA indication for DBS in practical reality will have a variable response profile, and it is critically important that the field shift from a disease specific model, to a more symptom specific model. Below are some examples of symptoms (or issues) that may be important for an individual patient seeking DBS:

Parkinson's Disease
- Tremor
- Rigidity
- Bradykinesia
- Gait
- Posture
- Balance (Falling)
- Speech
- Verbal Fluency
- Mood (Depression/Depressive Symptoms)
- Anxiety (Off Anxiety, Generalized Anxiety)
- Impulse Control Disorder
- Dopamine Dysregulation Syndrome
- Cognition
- Sexual Dysfunction
- On-off fluctuations
- Dyskinesia
- Potential for Medication Reduction
- Potential Effects of Genetic Status

Essential Tremor
- Distal Tremor (Fingers, Forearms)
- Proximal Tremor (Shoulders)
- Truncal Tremor
- Voice Tremor
- Head Tremor
- Gait
- Balance (Falling)
- Mood (Depression)
- Mood (Anxiety)
- Cognition
- Potential Effect of Genetic Status

Dystonia
- Focal Dystonia
- Segmental Dystonia
- Multi-Focal or Generalized Dystonia
- Mobile vs. Fixed Dystonia
- Primary vs. Secondary Dystonia
- Tardive Dystonia
- Potential Effect of Genetic Status

Obsessive Compulsive Disorder
- Medication Refractory Symptoms
- Behaviorally Refractory Symptoms
- Other Behavioral Symptoms
- Other Mood/Cognitive symptoms
- Potential Effect of Genetic Status

Does the Approach to DBS Change Based on the Symptom Profile

In a non-academic or private practice based setting it may not be immediately obvious to a referring physician or health care professional that the approach to DBS therapy can change based on an individual patient-specific symptom profile. This issue is not surprising, as FDA approval is typically associated with a disease state, and not a complex symptom profile. It is therefore very important to assemble a list of bothersome symptoms for an individual patient. Once the list is assembled, the next step is a discussion with patients and families the about the potential for a response to DBS, and for the discussion to be directed toward each symptom. In complex cases, a full patient-doctor discussion may need to be deferred until a meeting of the DBS interdisciplinary board has been afforded sufficient time to carefully consider the case.

In PD, the motor symptoms that respond to on-off dopaminergic testing are known to have the greatest potential for improvement following DBS[6)7)9)]. In addition, patients with medication resistant tremor may also improve with this therapy. DBS is a potentially powerful treatment for on-off fluctuations, and for dyskinesia. DBS has not been particularly effective for gait, balance, and falling issues, though in select cases where it can be demonstrated that these symptoms improve in the best "on" dopaminergic medication state, there may be potential for improvement[6)7)9)].

PD Depressive symptoms may improve slightly post-DBS. Anxiety, unlike depression, is more complex and it is usually difficult to predict a positive or negative response to DBS. If anxiety clearly improves or resolves in the dopaminergic "on" medication state it may improve with DBS[3)10)]. Most expert centers are cautious in operating on anxious patients without psychiatric support, particularly if the patient has been diagnosed with a generalized anxiety disorder.

Other issues also may complicate discussions of what will, and will not respond to DBS. Impulse control disorder and dopamine dysregulation syndrome have in select cases improved post-DBS, but there has been no consistent pattern of improvement across cases, and there has been an alarming de novo post-operative emergence of these issues in some

cases[11]. These types of behavioral issues should be stabilized pre-operatively, and carefully followed post-operatively. Cognition, apathy, verbal fluency, and speech all may worsen post-DBS, and patients and families should be aware of these potential risks[12]. Finally, the role of DBS in addressing specific genetic forms of PD is unknown, however initial data has revealed a positive DBS experience for several common heritable mutations[13)~16)].

In ET, a single thalamic DBS lead is most effective against distal tremor (hands and arms). DBS has been observed to be much less effective against proximal tremor (shoulders). Head tremor, voice tremor, and truncal tremor can respond, but have a much less consistent response pattern. It is not uncommon for ET patients to complain of voice issues, verbal fluency problems, and gait/balance issues post-operatively, even if stimulation is effective against hand tremor[17)~19)]. Patients and families should be aware of the symptom profiles, and should also be aware of typical responses in ET DBS.

In dystonia, the operation has been shown to be most effective against generalized and segmental forms, with less known about focal and task specific dystonia. Tardive dystonia, primary dystonia, and non-fixed dystonia tend to respond well to therapy. Contractures and secondary dystonia have a less predictable response. In many cases pain improves, even if a contracture is present. To date, the DYT-1 genetic form of dystonia is known to respond very well to DBS, and less is known about other genetic forms of dystonia[20)~24)].

In OCD, the operation is performed for only a handful of patients in the overall disease population. Potential patients must have been diagnosed by an expert, and must have medication and behaviorally resistant symptoms. The symptom profile for DBS is less understood, and the outcome predictors remain to be defined. Specific genetic loci and their relationships to DBS outcome are also unknown. Though early in the OCD DBS experience, contamination symptoms have been documented to have a robust response to neuromodulation. It is now becoming clear that other manifestations of OCD can potentially exhibit a positive response, and more research is needed to elucidate response predictors. Euphoria, panic, anxiety, smiling and mania can emerge post-DBS, and may require intensive medication and device management. Hoarding and hoarders are not thought to respond as briskly to the current DBS approach[25)~28)], and information on "responders" is slowly emerging.

Target Choice and Laterality

Once patient specific symptoms have been identified, and the risk-benefit ratio has been addressed, then a DBS target must be chosen. An additional consideration is whether to perform bilateral or alternatively to perform a unilateral operation[29)]. Target specificity in DBS therapy has been evolving, but there are currently no absolute rules. In PD, recent randomized trials have revealed that the motor symptoms have a similar response with subthalamic (STN) or globus pallidus internus (GPi) DBS[10)30)]. Based on this recent literature, many practitioners will tailor a target choice based on "other" symptoms. For example some teams utilize GPi for severe dyskinesia or cognitive dysfunction. Other DBS teams will choose STN as a target when medication reduction is the biggest issue[3)]. The exact nuances of each target remain to be elucidated. Additionally, in PD, recent literature has suggested that 30-40% of patients may only require a single unilateral DBS lead implantation[29)].

The target for ET has largely remained the ventralis intermedius nucleus (VIM) of the thalamus, however recent work has revealed that the STN, and the ZI may also be viable options[31)]. Additionally, the hand tremor of ET may progress despite DBS implantation[32)], and a rescue lead approach may be required later in the course of the disease[33)]. Many patient with ET will only require a unilateral implantation.

The main target for dystonia DBS has been the GPi, however recent work has revealed that in a small, but potentially significant number of cases, parkinsonism has emerged[34)]. The STN has been emerging as a potential target for cervical, segmental, and some cases of generalized dystonia[35)]. The advantages of one target approach over another have not yet been fully elucidated. Finally, other targets (thalamus, ZI, etc.) and unilateral vs. bilateral vs. multi-lead approaches are under current study within dystonia populations.

The targets and approaches (unilateral vs. bilateral) for OCD DBS are still under intensive investigation. The anterior limb of the internal capsule and nucleus accumbens region have been the most studied[26)28)], although there is a recent randomized trial of STN DBS for OCD[36)]. There are several other targets and approaches under study, and one small study approached the utility of unilateral DBS[37)].

Conclusions

As DBS and electrical neuro-network modulation evolve there will be a noticeable shift from treating diseases, to treating specific symptoms. This shift will result in interdisciplinary DBS boards collecting and addressing symptom profiles for all potential DBS candidates. Based on symptom profile, a strategic personalized medicine approach can be un-

dertaken (including target(s), placement (unilateral vs. bilateral vs. multifocal DBS leads), pre-operative medication management, and post-operative medication, behavioral, and device management).

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