Deep Brain Stimulation in Parkinson’s Disease: Past, Present, and Future

Though it has been underutilized over the past two decades, deep brain stimulation is an effective intervention for many individuals with Parkinson’s disease.

With Mahlon DeLong, MD

Over the last 20 years, Deep Brain Stimulation (DBS) has been FDA approved and used to treat a variety of movement disorders, such as tremor, Parkinson’s disease (PD), and dystonia. It has also been explored for Tourette’s syndrome and other hyperkinetic disorders, as well as a variety of neuropsychiatric disorders. Although the greatest use of DBS has been in the treatment of Parkinson’s disease, even for this it remains arguably underutilized.

Recently, the FDA revised the indications for PD, approving DBS for use not only for “advanced disease,” but for people with Parkinson’s disease in the mid-phase of disease; particularly though with disease of at least four years duration and with recent onset of motor complications, or motor complications of longer-standing duration that are not adequately controlled with medication. In opening up DBS to a wider range of patients, this expanded indication potentially signals a new period in the overall trajectory of DBS and could also encourage its greater acceptance and adoption as an integral tool in the management of Parkinson’s disease.

Ahead, Mahlon DeLong, MD, Professor of Neurology at Emory University and renowned expert in Parkinson’s disease, examines the wider significance of DBS within the spectrum of Parkinson’s disease and its role both in treating and advancing our understanding of this disorder.

PHASES OF PARKINSON’S DISEASE

Parkinson’s disease is a progressive neurodegenerative disorder, with motor, autonomic, sleep, cognitive, and psychiatric aspects says Dr. DeLong. “While motor aspects are arguably its most prominent feature clinically, they represent the tip of the iceberg, so to speak” Often, the first clinically recognized indications of Parkinson’s are tremor, slowness of movement (bradykinesia), and muscular rigidity, most often presenting unilaterally. In the early phase the disease—within roughly the first five years or more—patients are usually successfully treated with levodopa and other anti-parkinson medications. “At this stage, treatment is often quite straightforward and most patients who have been correctly diagnosed tend to respond very well,” he explains. “Patients with atypical forms of Parkinson’s, such as multisystem atrophy (MSA), cortico-basal ganglia degeneration, and Progressive Supranuclear Palsy (PSP) may not respond as well to medical therapy and are also generally poorly responsive to DBS. Thus, to confirm the diagnosis, levodopa responsiveness is required for patients undergoing DBS as well as a period of five or more years of observation to rule out atypical forms, for which DBS is not indicated.”

After the initial “honeymoon” phase of Parkinson’s disease, which can last five years or more, a significant number of patients begin to have motor fluctuations, characterized by “wearing off” of the medication effect before the next dose, as well as the development of involuntary movements (dyskinesias) at peak dose or during
the end of dose period, according to Dr. DeLong. These motor fluctuations may become quite upsetting, disruptive, and difficult to control for many of patients. “During this mid-phase period, which may extend for 10 years or more, there is a slow progression of the disease and many patients’ physical symptoms worsen with decreasing quality of life,” Dr. DeLong observes. The “late” or advanced phase of Parkinson’s is associated with the development of levodopa refractory gait and balance difficulties, freezing of gait, as well as cognitive and behavioral effects. “Management of patients in the late stage of Parkinson’s disease is an even greater challenge, as many medications fail to consistently control motor fluctuations and non-motor aspects come to the fore. Thus, the need for new approaches and innovations is critical, and experimentation in a number of areas has been undertaken,” he says.

WHY DBS?

Before exploring how the new FDA indication for DBS will help patients in the mid-phase of disease, it’s important to first establish a context for DBS and more closely examine why it matters.

“The introduction of DBS over two decades ago has had a transformative effect on our understanding and approach to Parkinson’s disease, replacing the earlier approach of ablation (lesioning), in particular pallidotomy and thalamotomy,” says Dr. DeLong. “The implantation of stimulating electrodes has brought about the use of micro-electro recording of monitoring local field potential and combinations of physiological, neurophysiological, electrophysiological imaging, and pharmacologic approaches. In a sense, the information gathered in many cases from patients in the course of performing these surgeries along with parallel studies in animals, has taught researchers and physicians a great deal about Parkinson’s and functions of these parts of the brain,” he continues.

“In the early days of investigating DBS, we were able to test the findings derived from animal research to humans, and the use of recording has reinforced and added greatly to that.” As a result, physicians and researchers now understand the signs of Parkinsonism (tremor, slowness of movement, muscular rigidity, and flexed posture) resulting from loss of dopamine, as a disruption of circuits that engage specific networks within the basal ganglia, cortex, and brainstem. “With DBS, we target specific regions of different nodes of the basal ganglia motor network, whether in the subthalamic nucleus or the globus pallidus. Specifically, we now understand that the abnormal network activity includes abnormal patterns of cell discharge, including oscillations, synchrony, and discharge of neurons, in essence a replacement of normal independent function and action by the abnormal synchrony and discharge throughout the network, which disrupts downstream function in the brainstem and cortex,” notes Dr. DeLong. “Breaking up abnormal disruptive patterns of neuronal synchrony and oscillations can be done with ablation, as was shown initially, but is more safely, as well as reversibly and adjustably, with continuous high frequency deep brain stimulation.” Considerable progress is now being made in understanding and testing alternative forms of stimulation which may be even more effective and efficient than continuous stimulation—using altered pattern- ing and targeting of stimulation, according to Dr. DeLong. Moreover, “Alternative targets involving brainstem networks, alone and in combination with current targets, are being explored for treatment of the poorly responsive motor aspects of advanced PD, including freezing of gait and falls.”

As we have studied DBS, we have learned several lessons that have yet to be applied in patients, simply because we’re waiting for new designs of pacemaker devices and better electrodes to steer the current away from and to certain areas and be literate in ways that the conventional standard therapies have not. “Ultimately, the potential is for us to stimulate targeted areas while also gaining more information about brain dysfunction, biomarker signaling, or anything from the patient side, symptomatically.”

Additionally, Dr. DeLong points out, opportunities are now in place to begin to use closed loop stimulation, which is triggered by signs and symptoms or internal signals that will make this perhaps much more effective. “This may result in continued innovations via the development of better stimulation models that yield significant benefit.”

As for what this modality has taught us, Dr. DeLong believes that DBS has greatly enhanced physicians’ understanding of the mechanism of the disease, while also offering the possibility of better methods for managing it. “Clearly, the pipeline of new, better devices and technology is in place, which beckons the broadened use of this...
modality for Parkinson’s disease and other neurologic and psychiatric disorders,” he says.

With previous ablation-based approaches, which used radiofrequency or focused radiation and various kinds of cooling, the effects were generally irreversible and potentially also caused damage to areas not intended or of giving only adequate or partial benefit. DBS can produce the same benefits via stimulation by overriding and disrupting the abnormal activity, while delivering it in a way that’s adjustable and reversible, which, according to Dr. DeLong represents a tremendous refinement and also yields better outcomes. “With electrodes moving through brain with minimal, if any, significant disturbance, it’s now possible to explore neurological diseases in ways that were never possible previously,” he explains.

In the future, Dr. DeLong expects that continued innovation in technology will allow physicians to target specific networks pharmacologically, such as with the use of light and optogenetic approaches.

INCORPORATING DBS: BARRIERS AND OPPORTUNITIES

DBS has traditionally been used to treat motor complications of levodopa therapy in “advanced” PD and found to be highly effective in improving motor function by greatly reducing the dyskinesias and off times and improving quality of life, according to Dr. DeLong. However, it is now recognized that earlier intervention in the mid-phase of PD, with the onset of motor complications, may both improve motor function and impact quality of life more effectively than best medical therapy alone. Regarding its clinical application, Dr. DeLong says that DBS should be considered in patients at the “mid”-phase of disease, when dyskinesias begin to appear. “For these patients, DBS may offer impressive results.” In fact, the similarity the two approaches offer in terms of efficacy is remarkable. “The major advantage of DBS is that it provides similar benefits without the side effects of traditional therapies. DBS confers continuous stimulation, which can be particularly effective for ‘off’ times.” It also generally abolishes or greatly reduces the peak dose effects of dyskinesias, he says.

Additionally, in some instances, DBS can offer benefits that medication does not. For example, “With tremor, some patients do not respond at all to medication, whereas DBS has shown to be highly effective in this regard. When it comes to drug-induced dyskinesias, we have very few drugs that are effective.” According to Dr. DeLong, amantadine is arguably the only one that’s really proven to be of significance in this regard.

However, possibly the best illustration of the critical role DBS should play in Parkinson’s therapy is not how it compares to best medical therapy, but how DBS plus best medical therapy compare to best medical therapy alone.1,2 “Studies have shown that there are major benefits for not only motor aspects of Parkinson’s disease but also the quality of life measures, such as individuals being able to continue working and better preservation of social activities that they might otherwise withdraw from,” says Dr. DeLong. “As patients progress and have more significant motor fluctuations, many experience greater difficulty with daily living, work, social activities. There is also pronounced risk that they may become cut off from friends and family and engage in fewer social activities as the disease progresses.” Thus, the benefit of DBS extends well beyond clinical features and also encompasses the reduction of the stigma of Parkinson’s disease.

Regarding adverse events, Dr. DeLong observes that DBS carries a small, but significant risk to patients undergoing this procedure. “Overall, there is a one percent risk of bleeding and possible neurologic deficit, resulting from placement of the stimulating electrodes. There is also about a five percent risk of infection involving the pacemaker and leads over the first five years, as well as a small risk of mechanical or lead breakdown,” he observes. Therefore, the patient must weigh potential risks versus benefits in deciding on DBS.

DEEP BRAIN STIMULATION: RESOURCES

To learn more about Deep Brain Stimulation, Medtronic’s website (www.medtronic.com) contains numerous resources for physicians, including information on acquiring training as well as patient selection. Additionally, the site offers access to peer presentations on DBS, procedure videos, details on reimbursement and prior authorization, as well as patient education resources for both pre- and post-implant care. Physicians can also find guidelines and manuals for various models.

PATIENT AWARENESS AND COMMUNICATION

One problem that has become very clear over the last two decades since DBS has been available is its underutilization. Put simply, the numbers of patients who are treated with DBS versus the number of patients who would benefit from it are not at all proportional, according to Dr. DeLong. Particularly with the expanded indication, he believes that more patients should be considered for DBS.

“Any time something new is introduced—a new idea, approach, theory, or discovery—there is always resistance and opposition initially,” says Dr. DeLong. Right now,
one of the key factors to the underuse of DBS is lack of understanding and awareness. “Many patients who would benefit from this modality know very little about it and are not aware of its availability and the opportunities it presents. Whether this can be attributed to unwillingness from some physicians to consider DBS or patients who would prefer a more traditional approach is difficult to say,” he notes. “In all likelihood, there is probably an element of both.”

Regarding patient awareness, while there are certainly avenues for patients to learn about DBS, many of these are not highly visible. “Patient support groups, for example, are a great place for individuals to hear first-hand experiences from others who have undergone the procedure. But patients need to first know of DBS before they go looking to learn more about it, and this can be a difficult first step.” From the physician side, there appear to be pronounced barriers to referral, the reasons for which are difficult to determine. “There is perhaps some fear of an interventional modality such as DBS, given the risk involved,” Dr. DeLong explains.

It’s certainly possible that the new indication and the resulting increased visibility will open new doors to awareness for both physicians and patients. Specifically, the removal the word “advanced” from the description, suggesting that this modality is not just for late-stage disease, could lead to greater awareness for the availability and options for earlier utilization of DBS, both of which would be substantial.

“Over time we will likely see greater acceptance of DBS, not only due to the expanded indication but also because of the increasing amount of compelling data indicating its benefit,” says Dr. DeLong. “These benefits range from motor to non-motor aspects, as well as activity, daily living, and quality of life measures (which are quite broad), in addition to occupational benefits,” For instance, those treated with DBS have been shown to continue working significantly longer, suggesting that they’re better off than patients who have received best medical therapy alone, according to Dr. DeLong.

In fact, the substantial impact on quality of life is likely what will propel DBS into a more prominent position in the treatment landscape for Parkinson’s disease in coming years, Dr. DeLong suggests. “For patients, QOL is critical, not just in terms of dealing with the tremor or difficulty with motility and typical features of Parkinson’s, but also how their disease impacts their ability to keep working and keep their contacts, friends, and family,” he says. These relationships can become compromised given the stigma of Parkinson’s disease. “Often, patients are never sure when the effects of their medication are going to wear off and get frozen or stuck at work or shopping. Thus, by reducing the dyskinesias, the tremor, the fluctuations, and the unpredictability, DBS really can restore tremendous independence.”

Therefore, when speaking with patients who may benefit from DBS, Dr. DeLong notes that physicians should convey the extent to which DBS can improve QOL in the longer-term. “While it is essential that patients understand that DBS does not alter the course of illness and that progression still may occur, it is also important to emphasize that early intervention with DBS can significantly improve function for a longer time during the middle phase of disease,” he observes. “Ultimately, prevention of motor complications is what allows patients to continue working and having comfortable socialization, and to have a full range of independence and activities that they begin to lose otherwise.” Fortunately, Dr. DeLong points out, the recent expanded indication means that physicians and patients no longer need to wait until QOL is compromised to begin treatment.

According to Dr. DeLong, it is important to impart to candidates for DBS that the decision to move forward is not a medical decision so much as a personal quality of life decision. “I then outline the projected progression of motility issues, dyskinesias, and complications from medications, and how they can be quite significant. But I also explain how the benefit goes beyond these things, such that DBS can preserve other pieces that are compromised,” he says. “I emphasize that, while DBS is ‘brain surgery,’ it is

**THE BOTTOM LINE**

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really very minor surgery and often better thought of as a ‘procedure,’ while noting that the modality can provide long-term benefit for signs and symptoms as well as quality of life for greater that 10 to 15 years.”

AN IMPORTANT NEED

Over the years we have seen many things come and go within the scope of understanding and treating Parkinson’s disease, from new approaches and cell therapies, to stem cells and gene transfer, to name a few. None of these, however, have proven themselves to have staying power, according to Dr. DeLong. “Deep brain stimulation, on the other hand, has proven itself an effective intervention for the treatment of Parkinson’s disease, particularly in combination with medical therapies. In addition to offering necessary clinical benefit, it can also have a profound impact on a patient’s quality of life,” he says. “Although DBS has not been integrated into broader care regimens as prominently as the data warrants, it nonetheless remains an integral component in both understanding and managing Parkinson’s disease.” As physicians and researchers strive to better understand the cognitive aspects and other complications of late-stage disease, Dr. DeLong feels that DBS may also fill an important need in continuing to experiment with various approaches.

In addition, the recent FDA approval for a broader indication reflects an emerging role for DBS for significantly enhancing benefit in mid-phase disease. Thus, as we move forward, Dr. DeLong notes that it is important for physicians not only to educate patients but also to remain open to the potential benefits of DBS and build contacts with specialty centers where patients can access treatment. “Candidates for early DBS should be referred to experienced specialized centers providing multidisciplinary teams of movement disorder specialists, trained stereotaxic surgeons, psychiatrists, and physical therapists for assessment and evaluation,” he says. “Deep brain stimulation is an area in which physicians, surgeons and investigators make long-term career commitments, so it is incumbent on physicians to take advantage of these multidisciplinary networks and resources. This increases awareness and knowledge about DBS while also giving patients the best chance for long-term quality of life.”

Mahlon DeLong, MD, is a Professor of Neurology at Emory University and a renowned researcher and expert in the area of Parkinson’s disease.


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