Precision Medicine: How Advancements in Imaging, Delivery, and Patient Comfort are Increasing the Relevance of Deep Brain Stimulation

By Gian D. Pal, MD, MS

One of greatest challenges of managing Parkinson’s disease is finding the right balance of what the patient needs at a given time. When patients are early in the disease, we may or may not recommend medicine, depending on their level of disability. But since Parkinson’s disease is a progressive disorder, eventually patients will need pharmacologic treatment, with the current gold standard still being carbidopa/levodopa (CD/LD). Patients can take CD/LD and do reasonably well for some time, but as the disease progresses, they may develop motor fluctuations and discover that their medicine is not working as reliably as they would like; it may be delayed in its onset in terms of its efficacy, or they may have a dose failure or wearing off of the medication. Patients may reach a point where they cannot depend on the medicine to help control their motor skills, requiring it either very frequently or in higher doses over time, which can be very problematic.

Patients may also develop dyskinesia over time. These hyperkinetic movements are at least in part related to disease progression and cumulative CD/LD burden. This can be very unsightly for patients as well as painful and disruptive to their mobility and balance. Thus, patients often find themselves stuck between a rock and a hard place: If they don’t take the medicine they become stiff and immobile, and if they do take the medicine they may become very mobile but also have excessive movements. In other words, it can be very difficult to find that “sweet spot,” where they are well controlled, feeling good, and not too slow or too fast.

While medication helps bring some relief to patients with PD, it has nonetheless become clear that the available agents are not enough to sustain stability as the disease progresses. While increasing dosages of medicine may be necessary, it could also possibly worsen motor fluctuations and dyskinesia over time. Therefore, physicians should consider the potential benefits of surgical approaches, notably deep brain stimulation (DBS). Since DBS can do many of the same things as medicines but without many of the side effects, it can be part of the long-term solution for patients.

Discussing DBS as a potential option allows patients to learn more about this technology and perhaps consider it as a means of gaining more control over their lives.
Moreover, DBS allows patients to reduce their medication burden by 30 to 50 percent and sometimes even more.

**Innovations in DBS Technology**

While DBS has been part of the treatment armamentarium for several decades now, the rapid evolution of the technology continues to increase its relevance. For example, the operative time has been reduced significantly, and the number of tracks or passes performed per hemisphere has also been significantly reduced. The increasing number of tools is also allowing us to localize the target of interest in the brain and maximize the precision and accuracy of lead placement.

Significant strides have also occurred in imaging. In addition to neurophysiological data, intraoperative imaging—such as Intraoperative Computerized Tomography (CT), the O-arm (Medtronic), and intraoperative MRI—allow us to perform the surgery with more accuracy and precision. Initial data has shown that intraoperative MRI, for example, can provide very good accuracy and give very comparable outcomes to standard ways of doing the procedure. DBS centers, including our own, have had success with intraoperative CT, which is a little bit less of an investment and also allows for imaging guidance to optimize lead location. Emerging data also indicates that we can reduce the number of tracks or passes in the brain with the support of these innovations in imaging. This could potentially reduce the surgical risk, resulting in a procedure that’s more efficient and less time consuming.

Delivery mechanisms for stimulation are becoming increasingly sophisticated, as well. For many years, Medtronic was producing the only FDA-approved DBS system and though this system has many programming options, it is not without limitations. Now there are other companies like Boston Scientific and St. Jude Medical that are allowing for a more current steering and current shaping, which allows clinicians to maximize the benefits of stimulation within the target and minimize the side effects by avoiding stimulating neighboring structures. However, even with these new DBS systems, lead placement remains of utmost importance.

In addition to these innovations, new advances in signal processing are enabling us to learn more about the rhythms of the brain that are involved with PD, how PD makes the rhythms abnormal, and how DBS and medicine may alter those rhythms and bring them closer to what should be normal. Right now the type of system we use is an open loop mechanism of stimulation, meaning that we don’t get any signals while the stimulation is happening. It’s a uni-directional system in that the stimulation delivered is programmed accordingly. These systems deliver the same amount of energy throughout the treatment regardless of what the patient is feeling. With signal process/analysis, we’re trying to have the machine detect abnormal signals and then deliver stimulation in response. In other words, it’s a bi-directional or closed loop system that adapts to patients’ needs throughout the day.

These signal processing/analysis mechanisms are still in the clinical development phase, but much work has been devoted to their development so that we can potentially shift from open loop to closed loop systems. With these systems, we will be able to tailor stimulation to patients’ needs, offering optimal symptom control as well as a reduction in side effects. A secondary benefit of a bi-directional system is that it would likely extend the battery life of devices, given that they do not constantly stimulate the brain. Certainly, this rapid evolution of technology will have an impact on clinical care and research, and with more industry competition we can expect continued innovations in the DBS arena.

**Increasing Patient Comfort**

As imaging technology and delivery mechanisms grow more intricate and refined, patient comfort has also been the focus of many recent and forthcoming advances in DBS. One notable stride in the spectrum of the patient experience is the ability afforded by intraoperative MRI to allow physicians to perform DBS while patients are asleep. This change may broaden the reach of the procedure, particularly since patients who would never have considered the procedure due to the necessity of being awake may not consider it.

While asleep DBS is already in practice at some large centers in the US, we should bear in mind that this is a relatively recent advance and that awake DBS remains the standard of care for most centers. For patients who are wary of the procedure due to this, physicians should explain to them why they need to be awake. When patients are awake, the brain is able to provide physicians with reliable signals as to what is actually going on in the brain and it helps us to optimize where the lead is placed. The other advantage to awake DBS is we can get real-time feedback through test stimulation, so that we can determine both the benefits and side effects of stimulation. If the lead is not in the optimal location, the patient may have suboptimal results and not have adequate...
symptom control. In addition, a poorly placed lead can stimulate neighboring structures, potentially resulting in changes in speech, balance difficulties, etc.

Thus, while asleep DBS is exciting, performing the procedure while the patient is awake gives you and the patient the confidence that the lead is going into the best possible spot with most benefit and least amount of side effects. That’s why it is important to give patients context when discussing awake/asleep DBS. Since DBS is an investment in their future, getting it right the first try is of paramount importance.

Another technology that’s been used of late is frameless DBS, in which patients have implanted markers mounted to the skull instead of using the standard stereotactic frame. This is a nice innovation because it reduces patient discomfort and OR time, but it has not yet been fully accepted due to a steep learning curve and limited long-term data.

Innovations like asleep and frameless DBS may not enhance the result of the procedure, but it’s possible they could be attractive to patients who may be good candidates but remain hesitant for reasons of comfort. Since both of these advances are relatively new and require more research, patients exploring these options should go to a center that is well versed in these procedures and techniques. Patients should also recognize that this is new technology that will require more time for many physicians to gain the necessary experience.

### Identifying and Communicating with Candidates for DBS

Identifying patients for whom DBS would be most effective is essential. DBS has shown to offer relief particularly for patients who begin to develop motor fluctuations and/or dyskinesia, as it can give patients more ON time (when the medicine is working) without dyskinesia, significantly reducing those peaks and valleys they may typically experience throughout the day. For patients who experience dyskinesia, DBS can potentially reduce their medication burden significantly. In fact, by reducing the medicine, they can have a reduction or potential elimination of dyskinesia. Moreover, the stimulation can be programmed in such a way to have an anti-dyskinetic effect.

Another group of patients that might benefit from DBS are those with medication refractory parkinsonian tremor. A patient with this condition is often taking CD/LD and doing reasonably well but has a severe tremor. From a social standpoint, it can be embarrassing and puts the patient at a disadvantage at work or in social engagements. In these instances, CD/LD may be helping with mobility but not addressing tremor. DBS is an option for these patients because it can reduce or even eliminate tremor.

### Broaching the Topic

It is the physician’s responsibility to start a conversation about the procedure with patients who may be candidates for DBS, even if they may not be ready at the moment. Discussing DBS as a potential option allows patients to learn more about the technology and perhaps consider it as a means of gaining more control over their lives. During the conversation, consider tailoring the message based on the patient’s stage of disease and always be frank about risks and benefits.

Patients who are just beginning to develop problems of motor fluctuations or dyskinesia should be aware of all options available. I often tell them, “I’m not suggesting that we do this now, but I want you to be aware of options that we may consider in the future if we are not having optimal symptom control with medication alone.” This allows patients to become better familiarized with the procedure—its benefits and potential adverse events—while also letting them know that you’re not trying to push them toward it.

For more advanced patients, discussing DBS in the context of their options and the future is critical. One consideration is that the surgery tends to be performed in folks who are under the age of 70; this is not a hard and fast rule, but more of a general guideline. Nevertheless, there is a window of opportunity that patients should be aware of. For patients who already have a high levodopa burden, we should consider DBS as a possibility sooner rather than later, since it can have a very positive impact on their quality of life as the disease worsens. When patients develop significant cognitive disability from PD or their motor function is significantly impaired even when their medication is working well, an invasive surgery may not be appropriate. I have found that the notion of the “window of opportunity” is helpful for them to grapple with the disease process and why we recommend certain therapies or procedures.

Parkinson’s disease is such a complex disorder and therefore it can be very difficult to know definitively pinpoint...
the right time for surgery. After a firm relationship has been established between the general neurologist and the patient, it’s important to open the possibility to therapies such as DBS and refer patients who may be candidates sooner rather than later, so they can get information and learn about what it can and cannot do. Referring patients doesn’t mean you are advocating for the procedure, necessarily, and patients should know that, too. Since DBS is a fundamentally different kind of therapy, both patients and movement disorders specialists should have the opportunity to think about it and consider the right time for the therapy, or whether it will meet the expectations or goals patients want to accomplish.

One of the most essential services general neurologists can extend to our patients with Parkinson’s disease is to develop a relationship with a movement disorder specialist to refer patients for early consults on the newest innovations in the field. It is essential that general neurologists and movement disorder specialists work together to help patients make the best decisions about their care. Importantly, the role of the movement disorder specialist in this relationship is often in an advisory capacity, with the general neurologist actively directing day-to-day care of patients. However, establishing a team approach in which patients periodically follow up with specialists allows patients to keep informed about their options and have the most information possible as they make decisions about their care. Ideally, movement disorder specialists and general neurologists would connect periodically, as well, and discuss therapeutic paths for the patient. These relationships, therefore, are a true collaboration, and establishing them sooner may lead to better utilization of therapies such as DBS.

Surgical procedures are not for all patients with PD, nevertheless it’s important to identify those who might benefit from and offer information about it rather than treating it like a last resort. Referring early to a movement disorder specialist is a critical step to optimal care because it can help guide patients on the right time to consider an invasive treatment while the window of opportunity is still open.

Collaborating for the Future

When it comes to the treatment of Parkinson’s disease, patients and physicians should be proactive about the future. We are fortunate that so many innovations are taking place within this spectrum and that patients can interact more easily for support and care. The neurologist can also be part of that process to help counsel and advise patients on therapies that they should consider, even if those options are not for everybody. In the case of DBS, specifically, despite so many recent advances and the vast evidence in support of its benefits, it remains an underutilized treatment modality for patients with PD. Therefore, it is essential that physicians are informed about it and establish relationships with specialists who they can rely on to bridge patient care.

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