PMDF

THE PARKINSON'S AND MOVEMENT DISORDER FOUNDATION

Newsletter ☙ Spring 2019

The Parkinson's and Movement Disorder Foundation

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MOVE4U 5k Walk/Run Fundraiser Event

by Tien Nguyen

On Saturday, May 11th of Mother's Day weekend, the Parkinson's and Movement Disorder Foundation hosted our 9th annual MOVE4U 5k walk/ run fundraiser benefitting movement disorders such as Parkinson's disease, dystonia, and spasticity. With the expected chance of light rain that fortunately never showed at Mile Square Park, the morning weather ended up being perfect for our 5k fundraiser event. Many long-time supporters, along with new faces, came out to participate in the event. With the support of our sponsors and participants, we were able to raise over $33,000! Joining us, we had over 100 participants, volunteers, and sponsors come together to promote awareness and support for Parkinson's disease and other movement disorders. Dr. Kong Truong, one of PMDF's medical advisors, provided opening remarks, along with getting participants eager to start the race. Smiles and laughs were abundant on this fun-filled day, whether on or off of the racecourse, with children enjoying our giant games including Corn hole, Tic Tac Toe, Jenga, and Connect 4. Participants were also better able to keep track of their times with the LED race clock placed right next to the finish line.

After participants walked and ran across the finish line, everyone was able to get settled down, and enjoy the delicious lunch that included a variety of finger sandwiches and our fresh vegetable and fruit platters. While everyone was enjoying lunch, the 1st, 2nd, and 3rd place winners were announced. Our third place winner was in for a relaxing treat, with their prize being a gift certificate toward a one hour Hot Stone Massage from Hand & Stone Spa. Our second place runner up was gifted with 2 General Admission tickets to Six Flags Magic Mountain. Lastly our first place runner won an exciting helicopter tour for 2 overlooking the beautiful scenery Hollywood and Downtown Los Angeles has to offer. Registered participants were also automatically entered in a raffle prize giveaway with over 20 prizes that included gift cards ranging from Starbucks, Target, AMC Theaters, and more.

A huge thank you to all the volunteers who helped make this event a wonderful success including Key Club students from Magnolia High School, Heather Nguyen, Brandon Docherty, Jennifer Braganza, Meredith Linares, Isaac Estrada, and volunteers from the Parkinson's and Movement Disorder Institute. A special thank you to all of the companies who were kind enough to sponsor our annual event:

Abbott Laboratories
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UCB Pharmaceuticals
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President's Letter

Dear friends of PMDF,

We're excited about the success of our MOVE4U 5K walk/run fundraiser in May. Thanks to generous participants and sponsors, we raised over $25,000 (after expenses). See the article elsewhere in this newsletter for details, and check out our Facebook page (https://www.facebook.com/ThePMDF/) for pictures.

For our fall fundraiser, we are having another "no show" fundraiser. This allows you support our research program for only about half of the price of our traditional fundraiser. You can contribute using the envelope included with this newsletter, or using PayPal through our web site.

We look forward to hearing from you.

Be sure to read the excellent articles in this newsletter, about advances in deep brain stimulation and advances in Parkinson's medication delivery systems.

Sincerely,

Mark Wadsworth

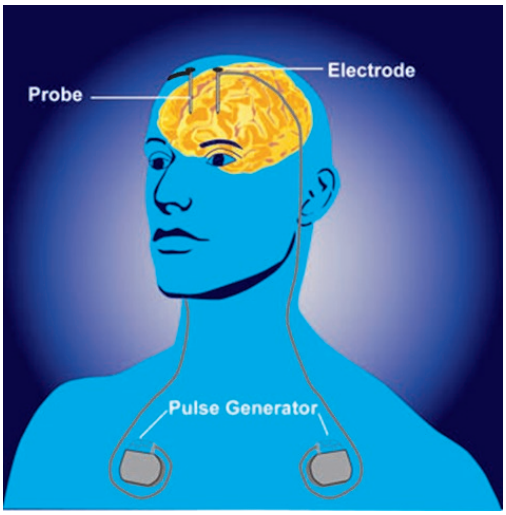
Mark Wadsworth
PMDF President

Deep Brain Stimulation in Dystonia and Parkinson's Disease– Exploring the Target Areas of the Brain

by April Ingram

It has been over 30 years since stimulation of specific, deep brain structures was found to improve the symptoms of movement disorders. Ten years later, in 1997, The Food and Drug Administration (FDA) approved deep brain stimulation (DBS) to an area of the brain called the ventral intermedius nucleus (VIM) as a treatment for people with tremor disorders (Parkinson's Disease and essential tremor).

DBS works by delivering carefully controlled, tiny electrical currents through precisely placed electrodes on one or both sides of the brain. The electrodes receive electrical signals through very thin wires from a small, pacemaker-like device that contains a battery and is placed under the skin in the chest or abdomen.



These small currents may stimulate and disrupt some of the abnormal neural firing patterns in brain areas that cause unwanted motor symptoms in people with movement disorders such as Parkinson's disease and dystonia. Many studies have shown that DBS has beneficial effects for people with dystonia as it can reduce the involuntary muscle contractions, movements, postures and tremors. Some studies have also reported that DBS can deliver a meaningful reduction in the pain caused by these symptoms.

The key decisions when making a DBS treatment plan are which area of the brain to target in order to optimize outcome, and if the individual would benefit from DBS to only one side of the brain or both.

As mentioned, the VIM was the first area of the brain that was approved for treatment with DBS for movement disorders. The VIM is located within the thalamus, a small structure in our brains above the brain stem. The main function of the thalamus is to communicate sensory and motor signals it receives to the cerebral cortex, where the majority of our brain processing occurs. As we know, the brain is complex and delicate. Any unwanted stimulation that occurs to nearby structures can cause unwelcome side effects. Some people who receive DBS to the VIM on both sides of their brain experience difficulties with fine motor control, swallowing, and speech. In order to remedy this, some devices, referred to as Directional DBS, allow for users to select from pre-set stimulation programs to provide options to better balance the beneficial effects of treatment while minimizing potential unwanted side effects.

In recent decades, fewer people are receiving DBS treatment to the VIM. It has become more common when treating dystonia for the DBS electrodes to be placed in an area known as the Globus Pallidus Interna (GPi). This treatment is also referred to as pallidal stimulation. In addition to dystonia, this is also a common area of DBS when treating akinetic-rigid Parkinson's. The GPi is located within the basal ganglia, which can be found on either side of the thalamus.

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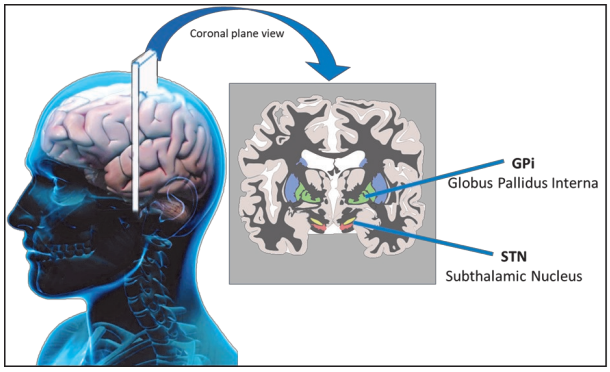
The subthalamic nucleus (STN) is also located in the basal ganglia, above the substantia nigra. DBS in this area is a common treatment for people with akinetic-rigid Parkinson's Disease. It reportedly allows for significant reduction in medication for many people, and improvement in symptoms for 50-70%.

Which is the better area of the brain to target, STN or GPi? A 2014 review article compared these areas in people with Parkinson's and found that DBS to the STN was more economical, superior in reducing medication, and required less frequent battery changes than GPi. GPi showed possible superiority in supressing dyskinesia and allowed for more flexibility when medication adjustments were needed. Studies have also reported that programming adjustments are easier to make in the GPi, and more people are able to remain unilateral (only receiving treatment to one



side of their brains) more often with GPi placement. The conclusion from this study was that both target areas have benefits, but most importantly, targets and approaches should always be tailored to the needs of the individual.

Other studies have compared DBS in the STN and GPi for the treatment of dystonia. In March 2019, Lin and colleagues published results showing that patients in both the GPi and STN groups demonstrated significant improvements in individual movement symptoms involving the face (eye, mouth), axis (neck, trunk), limbs (arms, legs), and speech. After 6 and 12 months, those who received GPi DBS had more significant improvements in their axis symptoms than those who had stimulation of the STN. However, larger improvements in speech were found in the STN treated group. Both groups had distinct improvements in their quality of life within the first month of treatment, and continued to improve up to 6 months after starting DBS treatment. Similar to the Parkinson's study conclusions, Dr. Lin and co-authors recommend that because both GPi DBS and STN DBS are safe and effective, selecting the best stimulation target should take into account the individual's specific symptoms and needs.

The Pedunculopontine Nucleus (PPN) is another area of the brain that is being investigated for DBS treatment of movement disorders. The PPN plays a role in gait—the way someone walks. Some small studies have demonstrated that low frequency stimulation of the PPN may be effective, although minor complications were reported in these small groups of people. Larger trials and ongoing research will be needed to confirm these findings.

Research is also ongoing to determine if there is a benefit from targeting a combination of areas, such as STN + PPN in order to meet the needs of individuals and their specific symptoms.

You and your doctor will be the best judges of whether deep brain stimulation is right for you.

More information can be found at the following websites:

DBS for Dystonia: https://www.dystonia.org.uk/deep-brain-stimulation

DBS for Parkinson's disease: https://www.parkinson.org/Understanding-Parkinsons/Treatment/Surgical-Treatment-Options/Deep-Brain-Stimulation

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Lin S, Wu Y, Li H, et al. Deep brain stimulation of the globus pallidus internus versus the subthalamic nucleus in isolated dystonia. J Neurosurg. 2019 Mar 8:1-12.

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Pump Therapies for Parkinson's Disease

by April Ingram

Carbidopa-levodopa is well recognized as the most effective treatment to manage the motor symptoms of Parkinson's Disease, and initially most people experience a good, stable response. Unfortunately, usually within five years, nearly half of people on treatment will begin to experience motor fluctuations and dyskinesia (uncontrolled, involuntary movement) between medication doses.

Individuals with Parkinson's describe the period of time when they are experiencing a good response to their medication as being "on" and when symptoms and involuntary movements return as being "off."

Typically, as the disease progresses, people may begin to notice their symptoms returning within 4 -5 hours after taking their medication. This is thought to occur because later in the disease course, the remaining dopamine nerve terminals in the brain are not able to store and release dopamine as effectively so there is increased reliance on levodopa from the blood plasma. Blood plasma levodopa levels can fluctuate and be unpredictable, often caused by factors that influence the absorption of medication in the intestinal tract. As Parkinson's progresses, stomach function can change and digestion can be slower or less predictable, affecting the way oral medication is absorbed into the blood stream.

When these fluctuating patterns of symptom control occur, the disease becomes more challenging to treat. This is when physicians begin to explore adjustments in medication or dosing, combination therapies, or even some more invasive options such as deep brain stimulation. A relatively new option for delivering medication to those with Parkinson's is by using a small infusion pump device.

Infusion pumps can provide people with slow, consistent dosing of their medications throughout the day, with the goal of reducing the number and intensity of between-dose motor symptom fluctuations. The device is programmed by the physician to provide customized dosing based on a person's individual need. The slow, low dosing eliminates the initial high dose peak when a medication is taken orally, with the intention of reducing "off" time and increasing "on" time.

Who would be considered a good candidate for infusion pump therapy? Recommendations suggest that people who have shown previously good response to levodopa medication but are no longer experiencing the same consistent benefit and symptom control between doses may be good candidates. Also, those who are experiencing severe motor fluctuations causing disability or reduced quality of life or those people that require levodopa dosing more than four times per day may be considered for pump infusion therapy.

There are two main types of battery-powered infusion pump devices used in Parkinson's treatment, continuous levodopa-carbidopa intestinal gel (LCIG) infusion delivered through a percutaneous gastrojejunostomy tube, and the continuous subcutaneous apomorphine infusion (CSAI). Both types of infusion have been shown to be effective at reducing "off" time and increasing "on" time.

The LCIG was approved by the FDA in January 2015. It is more invasive than CSAI and requires surgical placement of a percutaneous gastrojejunostomy tube. This means that a tube is inserted through the skin of the abdomen, through the abdominal wall into the stomach and then down into the duodenum into the jejunum of the small intestine.

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The tube requires diligent care at the tube entry site and daily flushing of the tube to prevent infection, which reportedly occurs in 18% of LCIG users. There have also been reports of a possible increased risk of neuropathy for those on LCIG therapy, so thorough laboratory testing and possible B12 supplementation may be required. The battery powered infusion pump is carried from the neck or waist in a small bag. LCIG is a carbidopa-levodopa enteral suspension (gel) (CLES; Duopa), that is continuously delivered through the tube for up to 16 hours per day. LCIG comes in the form of a cartridge containing carbidopa 4.6 mg and levodopa 20 mg per 1 mL of gel. At night, LCIG users disconnect the cartridge containing the medication, and in the morning they replace it with a new cartridge as they start their day. Some people on the 16 hour infusion will take an oral dose of carbidopa-levodopa at night time.

In the morning a larger bolus dose (100 to 200 mg levodopa, over 10 to 30 minutes) is delivered, followed by lower maintenance doses (20 to 200 mg/hour levodopa) throughout the day. It is possible to deliver extra bolus doses if they are needed to manage any breakthrough symptoms that aren't controlled by the continuous dosing.

Studies have shown that when LCIG was compared with oral immediate-release carbidopa-levodopa, those that used LCIG had their "off" time reduced by 4 hours (compared to 2.1 with the oral treatment) and the average "on" time without dyskinesia symptoms was 4.1 hours (compared to 2.2 hours for oral medication). In other observational studies, people with Parkinson's have reported between 40% and 80% reduction in "off" time with LCIG treatment.

Apomorphine hydrochloride has been shown to be beneficial to many with Parkinson's, but is often administered on a trial basis, initially, before moving directly to infusion, to see what the benefits are for a particular individual. The CSAI involves non-surgical placement of a thin infusion line and needle just below the skin, into the fatty tissue of the abdomen, upper arm or upper leg. Similar to LCIG, the battery-powered pump can be attached to a strap, worn around the waist or neck. In order to reduce the risk of infection, special care needs to be taken at the injection site. Other common side effects have included nausea and formation of skin nodules at the infusion site. CSAI may also cause severe episodes of low blood pressure (hypotension), so prior to beginning CSAI a test dose of apomorphine is administered to assess the blood pressure response.

In countries where CSAI therapy is available, dosing cartridges contain 10 mg/mL or 20 mg/mL apomorphine hydrochloride. Similar to LCIG, there is typically a morning dose, followed by a lower maintenance dose and extra bolus doses if needed to manage breakthrough symptoms.

In a clinical study that compared CSAI to infusion of a placebo over a 12 week period, those that received the apomorphine infusion reported a reduction in "off" time of 2.5 hours (compared to 0.6 hours for placebo group) and an increase in "on" time of approximately two hours.

The pump devices have been designed with the challenges of those with Parkinson's in mind, including very few, easy to press buttons and a large, easy to see display. The dosing flow rate is usually pre-programmed, with the allowance for extra bolus doses, and refilling the device can be simply done by replacing a cartridge.

There is no evidence that these pump therapies can slow the progression of the underlying neurodegenerative process; however, people have reported that this type of therapy has improved their ability to people to live independently in their own homes for many more years or opportunities to return to work.

You and your doctor are the best judges of whether pump therapy is right for you. More information about pump therapy for Parkinson's disease is available at the following website: https://www.parkinson.org/Understanding-Parkinsons/Treatment/Surgical-Treatment-Options/Duopa

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OUR MISSION

To support basic and clinical research into the causes, treatments and cures for Parkinson's disease and other movement disorders such as dystonia, myoclonus, spasticity, and tremor.

The Parkinson's and Movement Disorder Foundation is committed to working with other organizations that have similar philosophies in an effort to bring together expertise from both basic and clinical science perspectives.

We are dedicated to enhancing the quality of life for those who suffer from movement disorders and their families, through research, education, and community outreach.