DEMENTIA WITH LEWY BODIES: IN THE NEWS AND IN THE CLINIC

Written by Rachel Dolhun, MD
Medical Communications, The Michael J. Fox Foundation for Parkinson’s Research

Reviewed by Irene Hegeman Richard, MD
Professor of Neurology and Psychiatry, University of Rochester

December 15, 2014

ABSTRACT

Dementia is a global issue with implications for both individual families and society as a whole. Estimates hold that approximately 65 million people worldwide will be diagnosed with dementia by the year 2030. Dementia with Lewy bodies (DLB) is the second most common cause of neurodegenerative dementia. Primary care providers and general neurologists often are the initial contact for diagnosis; they then either manage patients and families independently or support them in conjunction with movement disorder or cognitive specialists. Regardless of their role on the health care team, all clinicians should be familiar with the nuances of this complicated disease.

The Scope of the Problem

Dementia with Lewy bodies (DLB) has been in the news since it was revealed that Robin Williams suffered hallucinations, paranoia and parkinsonism secondary to the condition. Dementia has also been in the spotlight given that November was National Caregivers Month. With widespread reporting on these topics by television media and Internet sources, clinicians are spending a lot of time correcting or clarifying information for patients and families who wonder whether they, too, will be robbed of their memories and ability to carry out activities of daily living by dementia. Physicians must be prepared to face these concerns and present a realistic, but not hopeless, picture of this disease.

DLB affects more than 1 million people in the United States and is second only to Alzheimer’s dementia (AD) on the list of neurodegenerative causes of dementia. With the aging population, that number is expected to grow exponentially in accordance with what some have referred to as the “silver tsunami.” Dementia will continue to upend the lives of even more patients and families, and our nation and current health care system must prepare to absorb the additional stress.

This article provides general guidelines regarding diagnosis and management of DLB, particularly in relation to idiopathic Parkinson’s disease (PD) with associated dementia (sometimes referred to as PDD). Family and caregiver issues are addressed and ongoing research in Dementia with Lewy bodies is briefly covered.

Maintain a High Index of Suspicion for Dementia with Lewy Bodies

Dementia with Lewy bodies can present acutely or subacutely. Minor surgical procedures; illnesses, particularly those requiring hospitalization; or medications, such as narcotics, might trigger delirium, characterized by agitation, confusion and possible psychosis. Reflecting then on the preceding months to years, families will frequently identify mild cognitive problems that had previously...
been attributed to aging or other conditions. Sometimes a spouse recognizes short-term memory issues or personality changes of which the patient is unaware or in denial. In other cases, a physician witnesses the unfolding of disease over time, from subtler concerns of difficulty multitasking or following directions along a continuum to fulminant dementia.

The central features of DLB are parkinsonism (bradykinesia, rigidity or tremor) and cognitive dysfunction. The latter develops prior to or within one year of motor symptoms and primarily influences attention, executive function and visuospatial domains. Consistent with dementia of any type, more than one aspect of cognition is impaired to a level that interferes with the patient’s daily, occupational or social functioning. While it is a progressive illness, DLB is characterized by fluctuations in cognition and levels of consciousness. A person can be nearly lucid one moment and completely confused the next. Spontaneous visual hallucinations (i.e., not necessarily precipitated by medication) are very common in DLB, and delusions, agitation or other behavioral disturbances may also occur. Autonomic impairment is not uncommon and may include urinary dysfunction and orthostatic hypotension. Patients with DLB may experience falls early in the disease course.

As with most neurodegenerative diseases, DLB is thought to result from a constellation of genetics, environmental factors and aging.

The differential diagnosis of DLB is broad. Reversible causes of cognitive impairment—vitamin B12 deficiency, thyroid hormone abnormalities, syphilis, pseudodementia secondary to depression, structural lesions or normal pressure hydrocephalus—must be ruled out. Other possible etiologies of dementia to be considered include AD, PDD, vascular dementia, frontotemporal dementia (FTD) and prion-related disorders such as Creutzfeld-Jakob disease.

### Differentiating Dementia with Lewy Bodies from Parkinson’s-Associated Dementia

Because of the parkinsonism seen in dementia with Lewy bodies, PDD is usually high on the list of other possible causes. Separating the two can be difficult but relies on:

- the temporal correlation between onset of motor symptoms and cognitive deficits,
- the presence of spontaneous or severe hallucinations early in the disease course,
- and a tendency toward earlier falls and more significant autonomic dysfunction.

In PDD, significant cognitive deficits follow motor symptoms by several years—10, on average. An estimated 50-80% of people with PD will be afflicted with dementia. Although visual hallucinations and autonomic disturbances may be present in both conditions, they tend to be more prominent and present earlier in DLB.

### Diagnosing Dementia with Lewy Bodies

The diagnosis of DLB—obviously serious and life-changing—rests on clinical expertise. The lack of confirmatory testing understandably makes everyone a bit uneasy. A formal neuropsychological evaluation can provide supportive data regarding the degree and pattern of cognitive dysfunction. Unfortunately the duration and intensity of testing, along with cost, can serve as deterrents. Brain PET or SPECT perfusion imaging are sometimes contemplated, but financial and geographic constraints—and the fact that results don’t change management—limit their utility. In addition, DAT scanning does not at present distinguish among the various neurodegenerative parkinsonian conditions. The Mini Mental Status Examination (MMSE) can monitor progression of disease when repeatedly administered over time, but, for screening purposes, The Montreal Cognitive Assessment (MoCA) is a more appropriate tool.

DLB can be verified only at autopsy. Lewy bodies—aggregates of abnormally folded alpha-synuclein, ubiquitin and other proteins—are widely distributed throughout the brain but are densest in the cortex. Of note, these pathological clusters are present in idiopathic PD and PDD as well but to a different degree and dissemination. The brains of patients with DLB also demonstrate loss of neurons, vascular abnormalities and basal forebrain cholinergic deficits. Interestingly, the beta-amyloid plaques and phosphorylated tau protein tangles of Alzheimer’s disease are seen in all of these conditions as well.

### Treatment Is Symptomatic and Supportive

No disease-modifying agent is available for DLB. Cholinesterase inhibitors—rivastigmine or donepezil—may provide a modest improvement in cognition and lessen hallucinations. Memantine has demonstrated benefit in small trials. Medications that can exacerbate mental status symptoms, such as anticholinergics, are best avoided or minimized. Neuroleptics—even atypicals—should be used cautiously, if at all. Patients with DLB are particularly sensitive to these agents and may experience worsening of parkinsonism and cognition. If antipsychotics are absolutely necessary, quetiapine is commonly used because it has the fewest extrapyramidal side effects. Clozapine is an option as well, but the risk of agranulocytosis...
limits its use. Newer therapies with a better side effect profile may be on the horizon. Pimavanserin, a selective serotonin inverse agonist, has recently received approval for Parkinson’s disease psychosis. Wakefulness promoting agents—modafinil or armodafinil—have been employed to increase alertness and limit daytime sleepiness but may worsen confusion and psychosis. SSRIs or SNRIs may be used to treat associated depression and anxiety. Levodopa can be prescribed for parkinsonism, but patients do not generally experience a robust response. In addition, levodopa may be more likely to induce psychosis or confusion in DBL patients. Dopamine agonists are rarely, if ever, used. For sleep disturbances and REM sleep behavior disorder (RBD), low doses of as-needed benzodiazepines could be considered, taking into account the inherent risks of sedation and falls. Many clinicians have begun to try melatonin first for insomnia and RBD as it is less likely to precipitate delirium or imbalance.

**Active Research Is Ongoing**

Many clinical trials surrounding the diagnosis and management of DBL are under way. European studies are recruiting patients for deep brain stimulation of the nucleus basalis of Meynert. One U.S. study is looking to examine whether treadmill walking can improve mobility and decrease falls. Another is attempting to repurpose nilotinib—a tyrosine kinase inhibitor currently approved for chronic myelogenous leukemia—to clear Lewy bodies and slow disease progression.

Participation in clinical trials allows patients, families and friends to take a proactive approach to a disease that may otherwise feel hopeless. Fox Trial Finder is a great resource to match patients, based on a de-identified medical profile, to available recruiting studies. Post-mortem brain donation is a possibility as well but needs to be considered before death; many centers require office visits and examinations so that autopsy findings can be correlated with clinical symptoms.

**Dementia with Lewy Bodies Touches an Entire Family**

In the course of the disease, a significant other switches from partner to primary caregiver and family members are called upon for ancillary physical, financial and emotional aid. Everyone involved must adapt to the patient’s progressive disease and changing needs.

A person with DBL is apt to require some level of supervision around the clock, but this depends on the stage of disease. The home environment and caregivers should remain familiar. Hearing loss or visual impairment must be remedied so as not to aggravate confusion and hallucinations. Driving is unlikely to be safe, but patients may argue for their privileges, even just to get to church or the local store. In these cases, an independent driving assessment, as offered by a rehabilitation center or AAA, is beneficial.

To minimize confusion and agitation, patients should adopt a regular daily routine and sleep schedule. Keeping a drowsy person awake by day and calm in bed despite hallucinations or REM sleep behavior disorder at night is definitely easier said than done. Planned daytime activities, like exercise or social interaction at a senior center, and limitation of daytime napping may help. Bed alarms, which sound when a patient gets up at night, can alert a sleeping care partner.

Doors must remain locked at all times to prevent outside wandering. An identification bracelet should be worn. To ensure patient and family safety, weapons, power tools and toxic chemicals need to be locked up or removed from the home.

Therapists are a necessary part of the professional care team. Physical and occupational therapists manage motor symptoms, gait instability and falls. They recommend adjustments and adaptations to improve home safety—removal of loose rugs and cords that can cause tripping; a bedside commode to prevent unsteady nighttime ambulation; and a hospital bed, chair lift or bathroom grab bars for ease of transfer and increased stability. They may suggest appropriate walking aids (taking into consideration that cognitive dysfunction will restrict use) and teach exercises to improve strength and range of motion. Speech therapists can attend to dysphagia by completing a swallowing evaluation and modifying diet and mealtime postures.

**Difficult Conversations Early Can Ease Later Transitions**

As dementia progresses, the patient will require more intensive care and assistance with all activities of daily living. Dysphagia elevates risk of aspiration pneumonia; falls can lead to head trauma and hip fracture; and immobility may result in deep venous thrombosis, urinary tract infection or decubitus ulceration. Eventually, a caregiver may become unable to safely and adequately support the patient at home due to his or her own physical and/or mental limitations. This possibility should be discussed sooner rather than later so that choices can be made before an urgent situation necessitates a pressured decision.
Social workers can educate families on long-term care options, insurance issues and financial considerations. They can also serve as liaisons to support groups and services.

Palliative care physicians offer extremely valuable input on symptom management in the advanced stages of dementia. Hospice care can be incorporated when the expected duration of life is six months or less.

Average survival time is five to eight years from determination of dementia, but, of course, this varies. A patient and family should be encouraged to complete advance directives—a living will and health care power of attorney paperwork—shortly after diagnosis. This topic is often overlooked but can be framed in a positive manner—advance directives give a patient power in a disease that otherwise strips control. Patients can be confident that their wishes for the later stages of life and death will be honored. Families can be comforted knowing they are fulfilling these desires.

**Don’t Overlook a Caregiver’s Needs**

Clearly a clinician’s primary focus is his or her patient. With this disease, however, ensuring the well-being of caregivers is a priority. They should be regularly asked about their own health, encouraged to schedule their own activities and remain socially active, and instructed to enlist the help of others for short-term respite or an uninterrupted night of sleep. Other family members can be invited to participate in doctor visits so that they can be informed about the disease and how they can assist their loved ones. Education is invaluable; physicians should direct families to appropriate online and print resources.

Caregiver participation in support groups, even online, is crucial for preventing isolation, validating struggles and learning coping strategies. The Lewy Body Dementia Association website is a good resource for both families and physicians. While Parkinson’s-specific, the Partners in Parkinson’s initiative from The Michael J. Fox Foundation and AbbVie may be beneficial in identifying and connecting with local and online support and resources.

In a disease in which symptomatic drug therapies leave much to be desired, the office visit becomes a major component of management. Gently leading a patient into the exam room and listening with an empathetic ear can relay powerful messages of care and concern. This alone may ease the burden of disease more than any prescription ever could and that might spark even a small bit of hope necessary for patients and families to continue the daily fight against dementia.

Rachel Dolhun, MD, is a movement disorder specialist who leads medical communications at The Michael J. Fox Foundation for Parkinson’s Research. Upon completing a fellowship in movement disorders at Vanderbilt University Medical Center, she worked in private practice prior to joining the Foundation. Her goal is to increase awareness, provide education and foster research engagement—among patients, communities and clinicians—surrounding Parkinson’s disease and related issues. Contact Dr. Dolhun at rdolhun@michaeljfox.org.

The Michael J. Fox Foundation is the largest nonprofit funder of Parkinson’s disease research worldwide. The Foundation is dedicated to finding a cure for Parkinson’s disease through an aggressively funded research agenda and to ensuring the development of improved therapies for those living with Parkinson’s today. Because patients are vital partners in this process, the Foundation works to mobilize volunteer engagement in research by providing education and direct research-related services to Parkinson’s clinicians, researchers, patients and families.
ABSTRACT

There’s bad news and good news for the Parkinson’s community: Parkinson’s disease is on the rise, but so are better treatments.

For almost 50 years, we’ve relied on levodopa as the gold standard of symptomatic therapy of Parkinson’s disease (PD). Within this standard, Sinemet (carbidopa/levodopa) is the most commonly prescribed medication, and for good reasons: it is safe, well-tolerated and effective for motor symptoms. Like every drug, though, levodopa has potential side effects, the hallmark being motor fluctuations. A desire to capitalize on the benefits and avoid these adverse effects has fueled research into new versions of the drug. Earlier this year, two new formulations of levodopa were approved, and several others are in mid-to-late stages of clinical testing.

Until the as-yet elusive curative therapy for PD is realized, we must continue to develop better symptomatic therapies and refine those, like levodopa, that are currently available.

Levodopa as We Currently Know It

Levodopa markedly improves motor symptoms for the majority of people with Parkinson’s disease. This leads to improvements in general quality of life and performance of daily activities, which in turn allows independence to be maintained and employment to be extended. Furthermore, widespread use of levodopa has decreased overall mortality and morbidity in the Parkinson’s population.

Still, for all the good this medication imparts, it has its limitations. For one, it unfortunately does little for the non-motor symptoms of PD. Secondly, as a consequence of its short half-life, levodopa requires frequent dosing. Even in conjunction with carbidopa, a decarboxylase inhibitor that prevents peripheral breakdown, the half-life is a mere 90 minutes and the duration of action only three to four hours. Finally, this recurrent cycle of medication kicking in and then wearing off with each administration leads to oscillations in plasma drug concentrations that, with chronic use (five to 10 years), contribute to motor complications in a good number of patients. Additional causative factors include higher total daily dosages of levodopa; the drug’s pulsatile, non-physiologic stimulation of degenerating neurons; and longer duration of PD.

Motor complications include both motor fluctuations (alterations between “on” periods of good mobility and “off” periods when
medication response is suboptimal) and dyskinesia (involuntary movements that arise most commonly at peak levodopa effect).

While these side effects can be disabling and debilitating, many people tolerate the medication quite well. Common problems—nausea and lightheadedness (due to orthostatic hypotension)—can often be managed with dosing or behavioral alterations. Taking levodopa with a carbohydrate snack, extra carbidopa (Lodosyn) or even domperidone (a peripheral dopamine antagonist available outside the United States) may combat nausea. If orthostatic hypotension is an issue, drinking more water, wearing compression stockings and elevating the head of the bed are initial steps that may be taken to counter dizziness and lightheadedness. Other approaches may include liberalization of dietary salt intake and adjustment of high blood pressure medications, which can be done in conjunction with the patient’s primary care doctor or cardiologist.

Levodopa itself is quite safe; it poses only a handful of possible pharmacological interactions and most of them are fairly benign. Vitamin B6 can lessen levodopa’s efficacy, and iron supplements may affect its absorption. Protein can also interfere with medication absorption, especially in patients with motor fluctuations. Since levodopa is an amino acid, it competes with other amino acids—from dietary protein—for uptake in the proximal small intestine. This, in addition to peripheral decarboxylation and delayed or inconsistent gastric emptying, can result in erratic absorption and bioavailability. For maximal benefit, levodopa should be taken 30 minutes prior to or 60 minutes after a meal. When scheduled every few hours, this instruction can generate frustration and noncompliance on the part of the patient.

### A Brief History of Levodopa Therapies

Throughout the 1960s, different administration routes and dosages of levodopa were tested in clinical trials. Once the safety, tolerability and efficacy of high-dose oral administration were demonstrated, levodopa was FDA-approved for use in PD in 1968. A few years later, in 1973, Sinemet was released. It wasn’t until 1991 that controlled-release Sinemet (Sinemet CR) came out. Almost 20 years following that, in 2010, Stalevo (carbidopa/levodopa and entacapone) reached pharmacy shelves. The latest developments in the United States occurred in early 2015 when two new formulations of carbidopa/levodopa—Rytary and Duopa—were approved. The latter has been available in Europe under the name Duodopa since 2004.

### Improving Upon an Old Standard

New drugs are always met with a combination of excitement and apprehension. Some patients and physicians are eager to try the “next best thing” while others choose to stick with what they know. Regardless of which camp one falls into, everyone would agree that having more treatment options, whether or not they are utilized, is preferable. This is especially true in a disease like Parkinson’s where advancing symptoms, medication side effects and comorbidities can restrict alternatives.

#### Rytary

Each capsule of Rytary contains immediate and extended-release beads of levodopa in a 4:1 ratio with carbidopa. Four different dosage strengths, ranging from 23.75/95 mg to 61.25/245 mg carbidopa/levodopa, are offered. The immediate-release beads take action in approximately 30 minutes and the sustained-release ones last four to six hours. The latter facilitate less frequent dosing (typically three, but up to five, times per day) and a steadier plasma levodopa concentration. Because higher total daily dosages of levodopa are recommended when switching from Sinemet IR or CR, three to four capsules of Rytary are often prescribed at each dosing administration.

Although levodopa-naïve patients can take Rytary, the most common users will probably be those with advancing disease who have inadequate control or motor fluctuations on their current regimen. In clinical trials evaluating Rytary, patients with motor fluctuations experienced reduced frequency of levodopa dosing and at least one less hour of “off” time per day. Patients who have difficulty swallowing pills will be able to take advantage of the fact that the capsule contents can be sprinkled onto applesauce or foods of similar consistency for consumption.

Greater patient and physician experience with Rytary will hopefully suggest the optimal titration and dosing schedule. Time will tell whether the formulation is truly able to lessen motor complications in the long run.

#### Duopa

Duopa is a gel suspension of carbidopa and immediate-release levodopa. It is designed for direct intestinal infusion through a percutaneous endoscopic gastrojejunostomy (PEG-J) tube. As its absorption is not affected by gastric mobility or emptying, more stable plasma levodopa concentrations can be achieved.

It is indicated for individuals with advanced PD who remain levodopa-responsive but suffer motor fluctuations. Various studies...
of this medication in advanced patients have shown a decrease in daily “off” time, gait dysfunction and freezing, along with improvements in non-motor symptoms, quality of life, dyskinesia severity, and “on” time without disabling dyskinesia. In those with three or more hours of “off” time per day, Duopa decreased “off” time and increased “on” time without dyskinesia by an average of four hours per day each.

This new formulation may be an option for those who do not want deep brain stimulation or cannot undergo the procedure because of significant postural instability, cognitive impairment or medical comorbidities. Those over the age of 70, who may get a less robust response from DBS, might also consider Duopa. The drug can be employed in people with mild to moderate dementia (MMSE > 20), although this necessitates a responsible caregiver to administer medication and PEG-J tube care. Duopa can also be provided via a nasojejunal (NJ) tube on a short-term basis (e.g., when a patient cannot tolerate oral intake for a temporary but extended amount of time) or for a trial period to evaluate drug response before committing to long-term therapy.

In order to start Duopa, patients must first transition to oral, immediate-release Sinemet. They must also undergo PEG-J tube placement—an outpatient procedure performed by a general surgeon, radiologist or gastroenterologist under moderate sedation or local anesthesia. Once the tube is in place, a cassette of Duopa, which contains 2000mg levodopa and 463mg carbidopa, is attached to a pump programmed to deliver a single morning dose, a continuous 16-hour infusion, and extra 20mg levodopa doses up to once every two hours as needed for rescue therapy of acute “off” periods.

In addition to the well-known side effects of levodopa, Duopa presents risks associated with the device itself, including malfunction, infection and intestinal complications (ileus, ischemia, hemorrhage, obstruction and perforation). One study showed the greatest rates of discontinuation were due to stoma infection or worsening dyskinesia not manageable with infusion reduction; these issues were highest among elderly patients and in the first year after the implant. Another trial noted an association between Duopa and a subacute or chronic sensory or sensorimotor axonal polyneuropathy. While this neuropathy has not been conclusively linked to vitamin B12 or folate deficiency, it’s worthwhile to measure these levels prior to starting Duopa and at regular intervals during therapy.

As with any new drug, time and experience will direct appropriate prescribing and will reveal the most common side effects and benefits.

New Frontiers in Motor Symptom Treatment

While clinicians fold these new offerings into their arsenals, researchers are working toward other formulations to control, and possibly even prevent, motor fluctuations.

Liquid Levodopa

ND0162L is a liquid formulation of carbidopa/levodopa that is delivered subcutaneously through a belt pump system similar to an insulin pump. A “pump patch” (an adhesive patch that delivers medication subcutaneously through microneedles) is also in parallel development. Fixed doses of the medication are infused over a 24-hour period, with lower dosages provided in the overnight hours.

This drug will likely be designated for patients with moderate to severe PD. Given the around-the-clock delivery, ND0162L may particularly benefit patients who struggle with frequent nighttime awakening due to Parkinson’s symptoms or who have pronounced difficulties upon awakening in the morning secondary to wearing off.

A Phase II trial in patients who had Parkinson’s for an average of eight years and had developed motor fluctuations demonstrated a high steady-state plasma levodopa concentration, reduction of motor fluctuations and a mean decrease in “off” time of two hours.

ND0162L is entering Phase III testing and could reach patients as early as 2018.

Higher dosages of liquid carbidopa/levodopa (ND0162H) are also being trialed in more advanced patients; this therapy will likely represent an alternative to current surgical interventions and Duopa.

Rescue Therapies for Sudden “Off” Periods

Rescue drugs for sudden, unpredictable “off” periods are sorely lacking. The only FDA-approved drug—the dopamine agonist apomorphine (Apokyn)—is given via subcutaneous injection. It can cause orthostasis, nausea and vomiting, and requires pre-treatment with anti-emetics and test-dose monitoring in the physician’s office. Even when tolerated, however, injections can be impractical to self-administer in the midst of an “off” period.

Two rescue drugs, described below, are in Phase III testing and could come to market as early as 2016.

APL-130277: The effects of this sublingual thin-film strip of apomorphine are seen in approximately 10 minutes and last up to 90
minutes. It has a lower incidence of nausea and hypotension than the injection and is much more easily administered. It has been tested at 10, 15 and 25mg doses.

**CVT-301**: Motor symptom relief from these capsules of levodopa inhalational powder, administered via a device similar to an asthma inhaler, occurs in about 10 minutes and lasts up to 60 minutes. Scientists are currently testing 35mg and 50mg doses. Of note, this therapy is solely levodopa—a patient must therefore be on concurrent carbidopa/levodopa or Lodosyn to prevent peripheral breakdown and side effects.

Despite these advancements, challenges with levodopa remain. For now, though, we have additional tools at our disposal and several more in the pipeline which will allow us to fine-tune the management of Parkinson’s symptoms and enable our patients to enjoy the best quality of life possible.

---

Rachel Dolhun, MD, is a movement disorder specialist who leads medical communications at The Michael J. Fox Foundation for Parkinson’s Research. Upon completing a fellowship in movement disorders at Vanderbilt University Medical Center, she worked in private practice prior to joining the Foundation. Her goal is to increase awareness, provide education and foster research engagement—among patients, communities and clinicians—surrounding Parkinson’s disease and related issues. Contact Dr. Dolhun at rdolhun@michaeljfox.org.

The Michael J. Fox Foundation is the largest nonprofit funder of Parkinson’s disease research worldwide. The Foundation is dedicated to finding a cure for Parkinson’s disease through an aggressively funded research agenda and to ensuring the development of improved therapies for those living with Parkinson’s today. Because patients are vital partners in this process, the Foundation works to mobilize volunteer engagement in research by providing education and direct research-related services to Parkinson’s clinicians, researchers, patients and families.
REFERENCES


Dystonia is the third most common movement disorder, after essential tremor and Parkinson’s disease (PD). Despite its prevalence, it is under-recognized and therefore undertreated.¹ Even patients with cervical dystonia, the most frequent form of isolated adult-onset focal dystonia, may see multiple providers over the course of longer than a year until accurate diagnosis is made and optimal therapy prescribed.² The combination of unique signs and symptoms, and lack of familiarity among physicians and patients alike can lead to missed or incorrect—including psychogenic—diagnoses.

Defining and Describing Dystonia

The term dystonia is used to describe abnormalities of motor control causing sustained or intermittent muscle contractions, resulting in repetitive postures or movements. These are usually consistently directional in nature. They are frequently twisting or turning movements and can be tremulous.³ Dystonia may be precipitated or worsened by voluntary action, such as walking or running. There may be a sensory trick, or “geste antagoniste” whereby a light touch, or the thought of a movement, may quiet the dystonia.

Dystonia can strike different body parts—the eyes (blepharospasm), lower face (oromandibular dystonia), voice (spasmodic dysphonia), neck (anterocollis, laterocollis or retrocollis), torso (truncal dystonia, camptocormia, pleurotonus), or extremities (limb dystonia or writer’s cramp in the arm). Infrequently, it may be specific for certain activities, such as with musician’s dystonia or golfer’s yip. It may affect only one region or may be generalized. The pulling and twisting movements are not always associated with discomfort but dystonia may cause pain, and the posturing may significantly interfere with normal function and diminish quality of life.⁴

Characterizing Dystonia

Consensus criteria for the classification of dystonia were refined in 2013 and involve assessment of two axes:

1.) Clinical characteristics: age at onset, body distribution, temporal pattern, and associated neurological or systemic features, and

2.) Etiology: nervous system pathology; pattern of inheritance, if any; mechanism of acquisition.³

This is where neuroimaging, genetic testing and/or medication review would enter in the appropriate clinical scenario. Imaging might evaluate for stroke; genetic testing may be done for DYT1 or
Wilson disease; and past use of typical or atypical dopamine antagonists could be reviewed.

Dystonia in Parkinson’s Disease

Dystonia may exist as a distinct condition, as in the case of “isolated dystonia,” in which there are no other neurological symptoms. Conversely, it can occur as just one feature of a more complex syndrome, such as atypical parkinsonism or idiopathic PD. Within Parkinson’s, dystonia can be the presenting sign, an associated symptom of the disease or temporally correlated with levodopa administration. The latter is the most typical demonstration of dystonia in Parkinson’s disease.5

Dystonia as a Presenting Symptom of Parkinson’s

Dystonia is not a classic presenting symptom of PD. However, because isolated lower limb dystonia uncommonly starts later in life, adult onset of such should raise concern for idiopathic Parkinson’s disease.6,7 Kinesiogenic foot dystonia—toe curling or foot inversion while exercising—has been reported among those with younger-onset disease, which is diagnosed prior to age 50.8,9 The lower extremity is the usual region afflicted by dystonia in Parkinson’s. Patients experience great toe dorsiflexion or foot inversion and/or plantar flexion, both of which can impair gait and cause cramping and aching pain.10

Other possible manifestations of dystonia in Parkinson’s are blepharospasm, bruxism, anterocollis, torticollis, upper extremity flexion and adduction, camptocormia, pleurotonus (Pisa syndrome), and anismus.5,11,12 A few of these are explored in more detail below.

Blepharospasm

Although more common in atypical parkinsonism, blepharospasm can be seen in patients with idiopathic Parkinson’s disease.13 This focal dystonia is characterized by involuntary contractures of the orbicularis oculi muscles.14 For patients who decline injections or experience incomplete relief with this treatment, oral medications—namely benzodiazepines, anticholinergics or spasmyotics (baclofen)—may be effective. Adjustments to dopaminergic therapy may be beneficial if symptoms worsen with wearing off in PD. Lubricant eye drops or ointments can be soothing for the sensation of eye irritation. Eyelid crutches or Lundie loops (glasses fitted with wire loops to press against the brow) may keep the lids open in the case of apraxia or serve as a sensory trick in blepharospasm.15

Anterocollis

Anterocollis refers to forward flexion of the neck out of proportion to trunk flexion. Some view it as a red flag for multiple system atrophy but it can occur in idiopathic PD and, perhaps, might simply indicate an axial form of the disease.16 Severe anterocollis results in an inability to lift the head off of the chest. Dysphagia, dysarthria and sialorrhea are often aggravated as a result. It can interfere with vision and gait, and understandably lead to pain. Supportive measures for the latter may include a soft cervical collar; physical and occupational therapy; and, in select patients, muscle relaxants. If anterocollis occurs exclusively as an “off” phenomenon, optimizing dopamine therapy should be the initial management. Movement disorders specialists may inject botulinum toxin into the bilateral anterior scalene and/or sternocleidomastoid (SCM) muscles, but with caveats. While side effects of botulinum toxin therapy may be minimized by utilizing EMG guidance and injecting the upper one-third of the SCMs, dysphagia in particular remains a significant risk. Surgical fusion of the cervical spine and deep brain stimulation (DBS) are occasionally effective. Anterocollis, especially when out of proportion in severity to other symptoms and present early on, should not automatically be attributed to idiopathic Parkinson’s—atypical parkinsonism, namely multiple system atrophy, should be considered. Furthermore, when neck extensor weakness is present, other diseases—inflammatory myopathy, myasthenia gravis or motor neuron disease—should be excluded.17,18

Camptocormia and Pleurotonus

Camptocormia and pleurotonus affect the torso—the former causes extreme anterior flexion (>45°); the latter is a lateral flexion and backward axial rotation. Both resolve upon lying supine and camptocormia also straightens with standing up against a wall, meaning the deformities are not fixed. This is in contrast to the spinal compression fractures, degenerative disc disease and scoliosis (lateral curvature of the spine) that many times occur in conjunction

The Michael J. Fox Foundation for Parkinson’s Research | Dystonia and Parkinson’s Disease
with and exacerbate these conditions. While there may be debate as to whether these are purely dystonic conditions (or if camptocormia represents a myopathy), most agree there is at least some element of dystonia that varies in severity in individual patients. If camptocormia and pleurotonus do present in idiopathic PD, they generally come on subacutely at least 7-8 years into the course of disease. People with camptocormia describe sensations of being pulled forward, abdominal tightening, lower back pain and/or dyspnea. Pleurotonus causes patients to initially tend to lean to one side while sitting and eventually this occurs while ambulating as well. They, too, complain of pain and dyspnea. These irregular postures interfere with mobility and vision and lead to gait instability and falls. As a general rule, camptocormia and pleurotonus are not dopamine-responsive. Treatment regimens are inconsistent and somewhat disappointing. Options include physical therapy; anticholinergic medications in younger patients; and botulinum toxin injections into dystonic musculature (rectus abdominis, iliopsoas or paraspinal muscles—depending on EMG and physical examination findings). DBS of the subthalamic nucleus (STN) or globus pallidus internus (GPI) provides relief in select patients. Spinal fusion surgery has been employed in medically-refractory cases but the risk of complication and need for revision is high. Orthotics and other devices can be worn to bring the stance more upright; however, caution must be exercised to not too suddenly overcorrect the posture and increase the chance of falling. Assistive devices minimize flexion, provide a sensory cue that transiently improves posture, and decrease fall risk.

**Remember the Differential Diagnosis**

The most likely explanation for each of the above dystonias in a person with Parkinson’s disease is the underlying neurodegenerative disorder. Still, other illnesses can arise concurrently. When symptoms come on acutely, the practitioner must look for metabolic changes, infectious causes, and structural or vascular etiologies, to name a few. A critical review of the medication list is always worthwhile—neuroleptics, anti-emetics, antidepressants, lithium, valproate, cholinesterase inhibitors, and even dopamine agonists (many of which are prescribed in advanced Parkinson’s) have all been reported to induce these dystonic syndromes. Finally, when any dystonia appears in the first few years of a suspected idiopathic PD, specifically if it is significant, rapidly progressive, and non-dopamine responsive, one must consider an atypical parkinsonian syndrome in the differential diagnosis.

**Dystonia in the Context of Levodopa Use**

The majority of patients with Parkinson’s take levodopa at some point in the course of their disease. Long-term use of this drug and disease progression are often accompanied by motor complications, which consist of motor fluctuations and dyskinesia. The former involve a return of parkinsonian signs and symptoms—slowly as medication wears off at the end of a dose, or suddenly, randomly, or unpredictably (as when individual medication doses fail to take effect). Dystonia can be a prominent part of these “off” periods but can also punctuate times when patients are “on” and medication may otherwise be working well.

Specific considerations for medication adjustments are described for the respective situations in which dystonia occurs below. If the symptoms are severely disabling and not remedied with medication changes, though, DBS may be an option. Surgery may improve “off” and early morning dystonia by providing continuous stimulation. It may alleviate peak-dose and diphasic dystonia by allowing dopaminergic medications to be lowered. While the GPI is the most standard target for isolated dystonia, it is not clearly more advantageous than STN for dystonia in Parkinson’s. As compared to DBS of GPI, however, that of the STN has been associated with a potentially greater reduction in dopaminergic dose, and this may be beneficial in the management of “on” phase dystonia.

**“Off” Dystonia**

When dystonia emerges in the context of chronic levodopa usage, it is most often in the “off” state and appears ipsilateral to the more severely parkinsonian side. This is when dopamine levels are low, as medication is wearing off at the end of dose or during the nighttime. Initial steps to combat wearing off dystonia typically involve increasing the levodopa dose and/or frequency of administration. Otherwise, the general management centers on longer-acting strategies like COMT-inhibitors, MAO-B inhibitors, and/or extended-release formulations of carbidopa/levodopa or dopamine agonists. Potential adverse effects, such as dyskinesia, must always be taken into account. For some patients, benzodiazepines or anticholinergics may be helpful. In the case of severe “off” dystonia, botulinum toxin injections may be required.

**Early Morning Dystonia**

This dystonia surfaces in the early morning hours, before the first dose of levodopa has taken effect. It most often impacts one or both of the lower extremities. It can last until the daytime medication kicks in or may spontaneously resolve. Symptoms can be mitigated with an
immediate-release formulation of levodopa, injection of apomorphine, and/or an extended-release formulation of a dopamine agonist.\textsuperscript{5,22}

**Peak-Dose Dystonia**

Dystonia may also occur during “on” periods. At peak-dose, when plasma dopamine levels are highest, motor function is optimal or complicated by dyskinesia.\textsuperscript{5,22} If dystonia happens during this time, levodopa dose may need to be decreased and the drug given more frequently. Amantadine may also aid in improving dyskinesia.

**Diphasic Dystonia**

Rarely, patients may exhibit a diphasic pattern of dystonia during both the “on” and “off” states. In this scenario, dystonia occurs when plasma dopamine levels are actually rising or falling rather than when they are at the trough or peak.\textsuperscript{5,22} Clinically, dystonia manifests at the beginning and end of a medication dose.\textsuperscript{21}

Diphasic dystonia represents a particularly difficult management issue. Attempting to lower the peak dopaminergic medication dose and employing the longer-acting medication tactics discussed for “off” dystonia are standard approaches. Patients who remain levodopa responsive but are plagued by intolerable drug side effects may be considered for DBS as discussed above.

Medication titration in each of these situations is obviously individualized. It is a trial and error process and communication between the patient and physician is paramount. The clinician must first determine when in the cycle of medication administration dystonia is occurring and the patient’s assistance is often necessary to chart this out. Sometimes this requires that the patient videotape or mimic their symptoms so that dystonia and dyskinesia can be correctly identified. Doing so ensures that the patient and physician are speaking the same language and discussing the same symptoms so that ideal medication adjustments can be made.

Dystonia in and of itself can be complicated to diagnose and manage, not to mention frustrating to live with on a daily basis. Adding Parkinson’s only makes it more challenging. Increasing awareness of dystonia among clinicians, patients, and society as a whole will hopefully translate to improved treatment and therefore overall quality of life for people with dystonia and Parkinson’s disease.

---

Reviewed by Rachel Saunders-Pullman, MD, MPH, MS, Associate Professor, Mount Sinai Beth Israel Medical Center, Icahn School of Medicine at Mount Sinai.

Rachel Dolhun, MD, is a movement disorders specialist who leads medical communications at The Michael J. Fox Foundation for Parkinson’s Research. Upon completing a fellowship in movement disorders at Vanderbilt University Medical Center, she worked in private practice for several years prior to joining the Foundation. Her goal in medical communications is to increase awareness, provide education and foster research engagement—among patients, communities and clinicians—surrounding Parkinson’s disease and related issues. Contact Dr. Dolhun at rdolhun@michaeljfox.org.

The Michael J. Fox Foundation is the largest nonprofit funder of Parkinson’s disease research worldwide. The Foundation is dedicated to finding a cure for Parkinson’s disease through an aggressively funded research agenda and to ensuring the development of improved therapies for those living with Parkinson’s today. Because patients are vital partners in this process, the Foundation works to mobilize volunteer engagement in research by providing education and direct research-related services to Parkinson’s clinicians, researchers, patients and families.
REFERENCES


Surgery for Parkinson’s disease (PD) was introduced in the 1930s and witnessed many adaptations as physicians gained knowledge, skill, and experience. Early pallidotomy and thalamotomy procedures created irreversible lesions—with varying levels of precision—via arterial ligation, thermal or chemical destruction, or radiofrequency ablation. Although not curative, thalamotomy had a dramatic effect on tremor and pallidotomy was variably effective for rigidity, bradykinesia and dystonia. With the widespread use of levodopa beginning in the late 1960s, though, lesioning procedures declined precipitously. Over time, motor complications from chronic levodopa usage, coupled with improved techniques renewed interest in surgical procedures.¹ Thalamotomy and pallidotomy are still performed in select cases, but they were eventually surpassed by adjustable neurostimulation.

Deep brain stimulation (DBS), which essentially mimics a lesional effect, was FDA-approved for PD in 2002 and quickly became the most frequently performed surgical procedure for Parkinson’s.²,³ In the appropriate candidate—one with moderate disease who remains responsive to levodopa but suffers debilitating complications (motor fluctuations or dyskinesia)—it can be extremely beneficial.

One of the more recent surgical technologies to enter the therapeutic pipeline for Parkinson’s is magnetic resonance–guided focused ultrasound (MRgFUS). This modality—currently in research trials—generates the same lesions as the aforementioned pallidotomies and thalamotomies but through an incisionless procedure.⁴

This article will review the latest developments and advances in Parkinson’s disease treatments, focusing specifically on DBS and magnetic resonance-guided focused ultrasound technology.
Present-day Deep Brain Stimulation

In the DBS procedure for Parkinson’s disease, electrodes are implanted uni- or bilaterally into either the globus pallidus interna (GPI) or subthalamic nucleus (STN). The choice is dependent on the experience and judgment of the neurologist and neurosurgeon and the individual patient’s symptoms and situation. Stimulation of either nucleus improves motor function and activities of daily living. When dystonia is prominent, GPI may be preferred; if the goal is greater reduction in medication dosages, STN is selected.

Once the electrodes are situated, they are connected to the implantable pulse generator (IPG), which contains the battery and neurostimulator. The IPG is placed subcutaneously, usually inferior to the clavicle (although sometimes in the abdomen) and delivers continuous, high-frequency trains of electrical pulses. Through a handheld device, the clinician can program a number of settings on the IPG:

- amplitude (voltage or current),
- polarity,
- pulse width or duration,
- frequency, and
- the “active” contacts (currently up to four on each lead), through which the stimulation is delivered.

Although both Medtronic and St. Jude Medical have FDA-approved DBS devices, only the Medtronic implants are commercially available. The basic structure and functionality of these systems are essentially the same. However, the Medtronic IPGs can deliver either constant voltage or constant current stimulation, whereas the St. Jude device only has capabilities for the latter. Constant current devices adjust output voltage to provide constant current stimulation irrespective of fluctuations in brain impedance (resistance). The current that constant voltage devices supply will vary if the impedance changes over time; this is a somewhat common occurrence since impedance falls in the months following the immediate postoperative period.

Regardless of which device or program is chosen, unique parameters are set for the individual patient and successively programmed to maximize benefit and limit side effects, while gradually adjusting medication. Following STN DBS, dopaminergic medications can generally be tapered but not discontinued entirely.

A well-selected candidate will experience solid symptomatic benefit, but every therapy has limitations and DBS is no exception. A few of the shortcomings are as follows:

- Reduced effectiveness on the management of certain symptoms over time. While 10-year outcomes of STN DBS showed maintained improvement on tremor and bradykinesia, the influence of DBS on motor fluctuations and dyskinesia declined over time. Its effect on axial motor symptoms exhibited an even greater loss of benefit in the same period.
  - Relatively little impact on freezing of gait, postural instability and many non-motor symptoms (e.g., dysphagia, dysarthria, urinary dysfunction), with potential worsening of speech and cognition, if either was impaired pre-operatively.
  - Contraindications, including dementia, severe mood disturbances and bleeding diatheses.
  - Requirement for IPG replacement procedures, which usually necessitate general anesthesia and incur additional hardware costs.
  - Potential hardware complications (e.g., lead tethering or fracture, or subluxation of the IPG).

Innovations in deep brain stimulation aim to address many of these issues with the goals of enhanced efficacy, reduced side effects, and prolonged battery life (with subsequently fewer replacement procedures). Advances include improvements to the present systems and programming options, development of the next generation of devices, and possibly stimulation of a novel target to treat postural instability and gait difficulty (PIGD).

Upgrading Stimulation Capabilities

Updates to present DBS systems and programs are characterized by attempts to “shape” and “steer” the delivered current. Such capabilities would allow the clinician to precisely direct electrical stimulation to the target of interest. The currently available programming approaches emit cylindrical or spherical stimulation fields that are distributed rather evenly around the orientation of the electrode. This somewhat indiscriminate delivery can cause unwanted stimulation of neighboring tissue and detract stimulation from the target tissue, leading to side effects and decreased efficacy.

Newer electrodes with a greater number of contacts and novel programming options permit the preferential distribution of current in a more specific direction. The ability to steer stimulation—guiding it away from an unfavorable brain area and toward a more efficacious location—would be particularly helpful in the setting of suboptimal lead placement, and might even prevent reoperation for repositioning. A small study of STN DBS using an investigational 32-contact electrode deemed steerable stimulation safe and tolerable and elevated the therapeutic window (amount of current that could be applied without worsening side effects).

The Vercise system (Boston Scientific Corporation), approved in Europe and in clinical trials in the United States, encompasses a number of these enhancements, including an electrode that houses...
Glutamatergic neurons have been linked to the initiation of Parkinson’s. Lower frequency settings have given mixed results on dysphagia, bradykinesia, postural control, and freezing of gait. Shorter pulse durations have lowered the required current output, which could increase the side effect threshold and prolong battery life by reducing the total amount of current needed over time.

New patterns of stimulation are being explored to see if they might more thoroughly suppress or disrupt the pathological rhythmic activity in the basal ganglia, and therefore more effectively manage the clinical symptoms of Parkinson’s disease. DBS is traditionally administered in a continuous, tonic, regular pattern, but recent trials have suggested that a non-regular manner of stimulation may be more beneficial to ease motor symptoms. Various models have been proposed but most aim to “desynchronize” the neurons with an initial high-amplitude pulse that primes them for a second, weaker stimulus. These patterns could deliver less overall energy, potentially translating to fewer adverse side effects and longer battery life.

Different Parameters and Patterns of Stimulation

Alternative DBS stimulation parameters have been examined to determine if they might more effectively alleviate motor symptoms of Parkinson’s. Lower frequency settings have given mixed results on dysphagia, bradykinesia, postural control, and freezing of gait. Shorter pulse durations have lowered the required current output, which could increase the side effect threshold and prolong battery life by reducing the total amount of current needed over time.

New patterns of stimulation are being explored to see if they might more thoroughly suppress or disrupt the pathological rhythmic activity in the basal ganglia, and therefore more effectively manage the clinical symptoms of Parkinson’s disease. DBS is traditionally administered in a continuous, tonic, regular pattern, but recent trials have suggested that a non-regular manner of stimulation may be more beneficial to ease motor symptoms. Various models have been proposed but most aim to “desynchronize” the neurons with an initial high-amplitude pulse that primes them for a second, weaker stimulus. These patterns could deliver less overall energy, potentially translating to fewer adverse side effects and longer battery life.

Development of the Next Generation of Neurostimulators

As manufacturers modify existing systems, the next generation of stimulators in development. Today’s DBS devices operate in a unidirectional, open-loop mode. Pre-programmed stimulation parameters are supplied in an uninterrupted manner, regardless of one’s fluctuating clinical status. Because of dynamic factors, such as alterations in medication levels, a patient is often subjected to periods of relative over- and under-stimulation, with associated stimulation-related adverse effects and suboptimal effects of DBS, respectively. Moreover, programming settings can be adjusted during scheduled clinical appointments based on limited information, such as the physician’s motor examination and patient’s interim history of symptom control.

Bidirectional, closed-loop DBS technology would address these issues. “Smart” systems could sense a patient’s unique neuronal signals and use this data to instantly modulate DBS settings and deliver stimulation on an as-needed basis (i.e., when freezing of gait or uncontrolled tremor occurs), rather than continuously. Adaptive devices could improve efficacy and efficiency, reducing side effects and prolonging battery life. By giving an inside look into individuals’ electrical signaling patterns and their responses to DBS, these devices could also afford insights into the pathophysiology of Parkinson’s disease and the mechanisms of DBS.

Multiple trials in Europe and the US are examining the above strategies in patients with Parkinson’s disease. Early results are encouraging. In fact, one study of unilateral closed-loop DBS showed that it was 30 percent more effective than conventional stimulation, and it decreased stimulation and power consumption requirements by approximately 50 percent.

Stimulation of Novel Targets

Since current DBS approaches do not adequately address PIGD in the majority of patients, researchers are beginning to target DBS to novel brain locations—the pedunculopontine nucleus (PPN) and adjacent pedunculopontine area (PPNa)—to determine if this might relieve axial symptoms, freezing of gait, and falls. The PPN and PPNa are part of the mesencephalic locomotor region (MLR), situated in the dorsal midbrain and contains GABA-ergic, glutamatergic and cholinergic neurons. The MLR plays a role in the initiation and modulation of gait and likely also the regulation of postural muscle tone. Additional support for the use of deep brain stimulation in the PPN and PPNa stems from the following:

- Glutamatergic neurons have been linked to the initiation of programmed movements and cholinergic neurons to the maintenance of steady-state locomotion.
- Cholinergic neurons in the PPN are significantly decreased in Parkinson’s patients.
- Patients with STN DBS who envisioned gait demonstrated activity changes in the MLR during PET scanning.

Promising though these targets seem, it is worth noting that clinical results have been inconsistent thus far. Differences in lead location and stimulation parameters, as well as the high variability of brainstem anatomy, may be to blame for this. Ongoing efforts strive to learn more about the PPN and its role in PD and determine the utility of targeting it for treatment. To this end, one clinical trial will place DBS devices (capable of both stimulating and recording neuronal signals) concurrently in both the GPI and PPNa for management of freezing of gait.

Magnetic Resonance-guided Focused Ultrasound

Magnetic resonance-guided focused ultrasound (MReFUS) uses innovative technology to make lesions without a surgical incision. In MReFUS, multiple beams of acoustic energy converge upon a small volume of tissue, destroying the target area and leaving nearby regions unharmed. Accompanying magnetic resonance imaging
allows structural visualization and provides thermal control of the lesioning process. The advantages of this intervention are that it can be performed without anesthesia or incisions; it is non-invasive; and it takes effect immediately. MRgFUS does not typically require repeat procedures unless the benefit wears off, and since there is no implanted hardware, there is no need for reprogramming or replacement surgeries. Although the procedure comes with risks, the rate of complications (such as infection and bleeding) has been low in preliminary studies.

The disadvantages, similar to other lesioning techniques, are that it is irreversible and permanent. Bilateral procedures are also typically avoided because dysphagia, dysarthria and/or cognitive dysfunction are unfortunately common sequelae. Early, small studies of MRgFUS in Parkinson’s patients indicated safety, tolerability, and effectiveness. Building upon these results, two types of trials are ongoing to evaluate the safety and efficacy of this therapy in PD. In non-randomized trials, unilateral MRgFUS pallidotomy of the GPi is being used for levodopa-induced dyskinesia. In placebo-controlled trials in which half of the subjects undergo a sham procedure, unilateral MRgFUS thalamotomy of the ventral intermediate nucleus is being done for medication-refractory tremor.

If approved, MRgFUS will expand the array of therapeutic options for patients with Parkinson’s disease with severe or advanced disease, principally those with contraindications to traditional surgeries or DBS.

In the future, this technique may also represent a cutting-edge way to deliver existing and new therapies to the brain. Pre-clinical work is using focused ultrasound to temporarily and reversibly disrupt the blood brain barrier. Combining this with drugs or gene, stem cell, or immuno-therapy could hypothetically improve permeability and therefore treatment efficacy.

**Innovations Expand Treatment Options**

Progress in deep brain stimulation and developments in focused ultrasound exemplify innovations in neurology. These surgical procedures complement the improvements occurring in available drugs.

Surgical interventions may never be for everyone with PD but they do provide symptomatic benefit for a large number of patients. Updating the current DBS systems, creating newer iterations of them, and improving surgical techniques will enrich the spectrum of symptomatic therapies for PD and the types and number of patients to whom they can be offered.

---

Rachel Dolhun, MD, is a movement disorders specialist who leads medical communications at The Michael J. Fox Foundation for Parkinson’s Research. Upon completing a fellowship in movement disorders at Vanderbilt University Medical Center, she worked in private practice prior to joining the Foundation. Her goal is to increase awareness, provide education and foster research engagement —among patients, communities and clinicians — surrounding Parkinson’s disease and related issues. Contact Dr. Dolhun at rdolhun@michaeljfox.org.

Article reviewed by Helen Brontë-Stewart, MD, MSE, John E. Cahill Family Professor, Department of Neurology and Neurological Sciences and Director, Stanford Movement Disorders Center, Stanford University School of Medicine.

The Michael J. Fox Foundation is the largest nonprofit funder of Parkinson’s disease research worldwide. The Foundation is dedicated to finding a cure for Parkinson’s disease through an aggressively funded research agenda and to ensuring the development of improved therapies for those living with Parkinson’s today. Because patients are vital partners in this process, the Foundation works to mobilize volunteer engagement in research by providing education and direct research-related services to Parkinson’s clinicians, researchers, patients and families.

REFERENCES


# TABLE 1: DBS INNOVATIONS

<table>
<thead>
<tr>
<th>Software</th>
<th>Hardware</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Steering and Shaping</td>
<td>Electrodes with higher number of contacts</td>
</tr>
<tr>
<td>Irregular Patterns of Pulse Delivery</td>
<td>Sensing/Recording electrodes</td>
</tr>
<tr>
<td>Current Steering and Shaping</td>
<td>Electrodes with higher number of contacts</td>
</tr>
<tr>
<td>Automatically adjusting output*</td>
<td></td>
</tr>
</tbody>
</table>

*Requires sensing electrodes
“Parkinsonism” and “parkinsonian” are terms broadly used to describe the motor features (i.e., bradykinesia, rigidity, resting tremor) typically associated with idiopathic Parkinson’s disease (PD). While there are other causes of parkinsonism (e.g., drugs that block dopamine receptors, cerebrovascular disease), the neurodegenerative diseases that can cause parkinsonism are deserving of deeper consideration.* These conditions, frequently referred to as the atypical parkinsonian—or Parkinson’s plus—syndromes (APS), include dementia with Lewy bodies (DLB), multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).

Early in the course, APS can be easily misdiagnosed as idiopathic PD because of the symptom overlap, lack of objective diagnostic biomarkers and, for some patients, a symptomatic improvement with levodopa. Waning medication benefit, development of additional characteristic signs and symptoms, and more rapid progression of disease may eventually differentiate these conditions from PD, although this can take years. Diagnosis is based solely on history and physical examination but ancillary testing—specifically neuroimaging—may support clinical impression and/or exclude conditions that may require (or respond better) to other treatments. Structural imaging (CT or MRI), for example, may reveal vascular disease or normal pressure hydrocephalus (both of which may present with clinical features similar to those seen in neurodegenerative parkinsonism). MRI may be normal or show mild diffuse atrophy in PD or DLB but demonstrate distinct patterns of atrophy in the other APS, particularly with advancing disease (e.g., midbrain atrophy in PSP). DaTscans, which approximate the presynaptic binding activity of dopamine transporters, may be helpful to distinguish neurodegenerative (PD or APS) from drug-induced or vascular forms of parkinsonism or essential tremor, but cannot differentiate among APS, or between them and PD.

Definitive diagnosis of APS can be made only through neuropathological confirmation, the hallmark of which is intracellular protein deposition. Abnormal accumulation of alpha-synuclein is characteristic of PD, DLB, and MSA (the synucleinopathies); tau protein aggregates in PSP and CBD (the tauopathies). The clinical relevance of differentiating synucleinopathies from tauopathies requires further study, but certain generalizations (e.g., the correlation of synucleopathies with premotor symptoms and autonomic dysfunction) may help clinicians focus on potentially relevant aspects of the history and physical examination and thereby narrow the differential diagnosis.

Regardless of diagnosis, however, no disease-modifying therapy has been demonstrated effective for any of the APS, so management is symptomatic and supportive. A variety of drugs are utilized to target individual symptoms—levodopa being the first-line for parkinsonism—and physical, occupational and speech therapy are often beneficial adjunctive treatments for motor and bulbar symptoms. These conditions represent a diagnostic and therapeutic challenge that demands a careful and comprehensive approach.
Synucleinopathies (DLB and MSA)

Multiple System Atrophy

Clinical Features. MSA often presents in the sixth decade with parkinsonism (MSA-P) but may, less commonly, occur in an alternate form characterized by cerebellar dysfunction (MSA-C). Both subtypes are associated with autonomic dysfunction. Parkinsonism, which tends to be—but is by no means exclusively—symmetric, manifests as bradykinesia with rigidity, gait and postural instability, and/or tremor. Tremor, if present, is more apt to be irregular and may be greater with posture and action rather than rest. Autonomic symptoms, which often precede motor symptoms, include orthostatic hypotension (OH) and urinary and/or erectile dysfunction (ED). Although PD patients can experience dysautonomia, that associated with MSA usually (but not always) presents earlier in the disease course and is more severe. OH due to autonomic impairment is demonstrated by a blood pressure drop upon arising (SBP > 20 mmHg and DBP > 10 mmHg) without the compensatory heart rate increase seen in patients who are simply volume depleted or treated with alpha-adrenergic blockers. It may be exacerbated by dopaminergic medications (i.e., levodopa or dopamine agonists). Genitourinary problems increase with aging, making ED and urinary disturbances nonspecific, but normal function of either would make MSA less likely. Symptoms are more severe in MSA (versus PD) and the type of urinary dysfunction is different—in PD it is most often frequency and urgency, whereas in MSA it is retention. Additional supportive features include characteristic postural abnormalities (e.g., lateral spinal flexion and/or disproportionate anterocollis), early bulbar dysfunction (e.g., dysphonia, dysarthria, dysphagia), and nighttime laryngeal stridor. Mild cognitive impairment involving memory and executive function may also be seen but dementia appears to be less common than in PD and is certainly not a fundamental feature as it is at some stage in most of the other APS. MSA progresses over an average of six to 10 years and death typically results from aspiration pneumonia or nocturnal cardiorespiratory arrest. Diagnosis. Diagnostic criteria for MSA, revised in 2008, provide guidelines for making a diagnosis on three levels of certainty—possible, probable or definite. At the core, MSA is an adult-onset (age greater than 30 years), sporadic, and progressive condition. Depending on whether it is possible or probable MSA, symptoms of autonomic failure, poorly levodopa-responsive parkinsonism or a cerebellar syndrome, and/or a characteristic clinical or neuroimaging abnormality are required. Definite MSA can be diagnosed only by neuropathological examination, which demonstrates degeneration of striatonigral and olivopontocerebellar structures along with profuse alpha-synuclein-positive glial cytoplasmic inclusions. Based on whether MSA is of the parkinsonian or cerebellar subtype, the brain MRI may show focal atrophy of the putamen, middle cerebellar peduncles, lower portion of the basis pontis, medulla and cerebellar hemispheres. T2 hyperintensity can also be seen in the basis pontis—the “hot cross bun sign”—and in the postero-lateral putamen. Structural changes may, unfortunately, be most evident when disease is well-established and diagnosis is no longer in doubt. Therefore, neuroimaging can typically support clinical suspicion, but not render an actual diagnosis. Autonomic function testing may be similarly helpful to aid with diagnosis and could also potentially serve as a prognostic marker.

Tauopathies (PSP and CBD)

Progressive Supranuclear Palsy

Clinical Features. The classical symptoms of PSP are postural and gait instability with falls, symmetric akinetic-rigid parkinsonism of the axial musculature, and vertical gaze paresis. Imbalance, gait difficulties and a tendency to fall backwards are the first and the most frequent symptoms of the disease, with a mean age of onset in the early to mid-60s. Gait is typically stiff and broad-based with truncal extension. Limitation of voluntary vertical eye movements leads to falls when descending stairs (due to downgaze palsy coupled with neck extension) and difficulty reading (secondary to problems scanning text). Visual disturbances (e.g., diplopia, blurred vision, photophobia) are typical complaints at disease onset or within the first year. Cognitive and/or behavioral changes—impaired executive function, loss of insight and apathy—usually begin within the first year as well. Other common features include bulbar symptoms (e.g., dysarthria, dysphagia, pseudobulbar affect) and blepharospasm.
Less frequently, PSP patients may exhibit an asymmetric, limb-predominant, levodopa-responsive parkinsonism (initially indistinguishable from idiopathic PD), pure akinesia with gait freezing (i.e., lack of rigidity or tremor), behavioral variant of frontotemporal dementia, progressive non-fluent aphasia or corticobasal syndrome (CBS). When (and if) vertical gaze palsy and postural instability and falls arise, these syndromes might be recognized as PSP. One exception is CBS, in which symptoms may remain clinically identical regardless of whether the underlying pathology is that of PSP or corticobasal degeneration.1,11 (See below.)

Length of survival with PSP is an average of five to eight years; death is most often a consequence of aspiration pneumonia.1,7,11

Diagnosis. Consensus guidelines, created in 1996, denote that PSP is a gradually progressive disorder with onset at age 40 or later. Diagnoses of probable or possible PSP are based on the presence of oculomotor dysfunction (vertical supranuclear gaze palsy and slowing of vertical saccades) and prominent postural instability with a tendency to fall within the first year of disease onset.11 Definite PSP is diagnosed histopathologically, when tau-positive neurofibrillary tangles in neurons and neuropil threads in neuronal processes, as well as accumulations of phosphorylated tau in astrocytes and oligodendrocytes, are found in a characteristic distribution throughout the brainstem and basal ganglia.1,11

Examination of eye movements typically reveals slowed vertical saccades, an intact vestibulo-ocular reflex and/or limited vertical gaze. A constricted downgaze is more specific for PSP (some limitation in upgaze occurs with aging and may be present in other neurodegenerative disorders).11 Other supportive physical examination findings include a positive pull test (and often also a spontaneous tendency to fall), upper motor neuron signs, decreased verbal fluency, perseveration and frontalis dystonia.1

Brain MRI may show midbrain atrophy, third ventricular dilatation and an intact pons, giving rise to the classic “hummingbird” or “penguin” sign. Superior cerebellar peduncle atrophy and/or increased FLAIR signal are sometimes also visualized.8,9

Corticobasal Degeneration

Clinical Features. CBD is a neuropathological disorder that expresses at least four different clinical phenotypes. The most common is corticobasal syndrome (CBS) and the others are frontal behavioral spatial syndrome (FBS), nonfluent/agrammatic variant of primary progressive aphasia (nPPA) and progressive supranuclear palsy syndrome (PSPS).12,13 Symptoms usually arise in the sixth or seventh decade and progress over an average of six to eight years.1,12 Death typically results from aspiration due to dysphagia.1

CBS is marked by motor symptoms—parkinsonism, dystonia and myoclonus—and lateralized cortical features.12,13 The parkinsonism is a strikingly asymmetric levodopa-resistant rigidity and bradykinesia, predominantly involving one upper extremity. Dystonia usually produces a fixed posture in which the arm is adducted at the shoulder, and the elbow, forearm and hand are flexed. It often results in pain, secondary contractures, palm lesions and/or functional limitations.13 Myoclonus may be focal, action or stimulus-sensitive; it can also be superimposed on tremor which, if present, is poorly characterized and usually unlike the classic resting tremor of PD.1,12 Gait abnormalities, postural instability and falls also occur in CBS, but not typically in the early stages of disease.12

Cortical symptoms of CBS may include one or more of the following:1,3,12

» Apraxia, or impaired performance of learned, skilled motor acts despite intact sensory, motor and language function. Ideomotor apraxia, specifically impacting the limbs, is the most frequent form in CBS. Orofacial muscles can also be involved, though, especially later in the course.14,15 Apraxia can be demonstrated by having patients perform a gesture (e.g., wave goodbye, use a hammer or blow out a match) although limb dystonia and parkinsonism can make accurate assessment challenging.12

» Alien limb phenomenon— involuntary motor activity of a limb combined with a feeling of estrangement from that limb.15 Movements are typically complex, unintentional and interfere with normal tasks. The limb may be described as foreign or as having a will of its own.12 If they occur, alien limb symptoms typically present an average of 12 months into the disease course.12
Cortical sensory loss, or inability to correctly interpret sensation despite intact primary sensory modalities. This can manifest as impairment of two-point discrimination, astereognosis, agraphesthesia and/or extinction to double simultaneous stimulation.1,16

Language impairments, such as aphasia or speech apraxia.

Cognitive disturbances, predominantly in executive function, which range from mild cognitive impairment at disease onset to frank dementia in later stages, with preservation of semantic memory.7 Behavioral changes and mood alterations may be associated.12

**Diagnosis.** CBD is a pathological diagnosis, characterized by widespread deposition of hyperphosphorylated tau in neurons, astrocytes and oligodendrocytes throughout the neocortex and basal ganglia.1,12 Criteria for the diagnosis of CBD were updated in 2013 to characterize the multiple clinical phenotypes of CBD (listed above) and potentially enable pre-mortem recognition of the disease. (This is in contrast to diagnosing CBS—a clinical syndrome with multiple underlying pathologies, including CBD, PSP and others.) The CBD guidelines specify an insidious onset of disease and minimum duration of one year along with gradual symptom progression. Age, family history of neurodegenerative disease, presence of tau genetic mutations, and specific symptoms characteristic of the individual CBD phenotypes are considered to make diagnoses of probable or possible CBD.3,12

Supplementary testing cannot diagnose CBD syndromes or CBS but could provide supportive evidence. In CBS, brain MRI may demonstrate asymmetric atrophy of the posterior frontal and parietal lobes, even in early stages of disease, and the lack of midbrain atrophy and basal ganglia changes may serve to differentiate it from PSP and other APS, respectively.8,9 Neuropsychological testing might also be beneficial to delineate cognitive deficits.

**Symptomatic Management of Atypical Parkinsonism**

**Parkinsonism.** Despite the fact that benefit is transient and is usually modest at best, levodopa is the first-line therapy for Parkinsonism in the APS. To adequately assess responsiveness, a trial of at least 1g/day levodopa (in combination with carbidopa) for a period of two to three months is recommended.3,11 High doses may not be tolerated, however, and in MSA, levodopa is likely to exacerbate orthostatic hypotension and induce early oro-facial dyskinesia or dystonia.2,3 Dopamine agonists, amantadine and MAO-B inhibitors may be alternatives to levodopa, but these have variable, and oftentimes limited, efficacy and are frequently poorly tolerated.1,2,3,13 Physical and occupational therapy (PT and OT) are important complementary components in the management of parkinsonism.

**Dystonia.** Botulinum toxin injections are a good option for focal dystonia—blepharospasm in PSP, upper extremity dystonia in CBD, and select cases of anterocollis and laryngeal stridor in MSA.7 Systemic side effects are usually minimal and treatment response is high.1 Oral agents (e.g., benzodiazepines, anticholinergics, muscle relaxants, baclofen) are rarely effective for dystonia in APS.1,13 PT and OT can be helpful adjuncts to pharmacologic therapy.

**Myoclonus.** Myoclonus—most commonly encountered in CBD—can often be alleviated with benzodiazepines (especially clonazepam) but levetiracetam, gabapentin and valproic acid may be alternative options.1,13

**Gait and Balance Impairment.** Even before gait disturbances and postural instability are present or prominent, physical and occupational therapy may be beneficial. Early in the course of APS, therapists can teach patients exercises to help maintain strength, flexibility and mobility, as well as enhance the performance of activities of daily living. They can also instruct patients in fall prevention and assess the need for an ambulation aid (i.e., cane or walker, sometimes weighted for PSP patients). In later phases of disease, therapists can perform home safety evaluations (and propose modifications and/or adaptive equipment to make daily routines safer and easier), train caregivers in range of motion exercises and direct proper wheelchair selection, if required.13

**Speech and Swallowing Disturbances.** Speech therapists can treat language dysfunction with speech exercises and suggest devices to facilitate communication. Dysphagia is addressed with recommendations for appropriate dietary consistency, behavioral adjustments at mealtimes, and/or...
Techniques to promote adequate nutrition and reduce the risk of aspiration. Percutaneous endoscopic gastrostomy (PEG) tubes are not always necessary, but it is generally worthwhile to consider them proactively rather than after choking or overt aspiration has occurred, as these can result in potentially fatal pneumonia. Raising the possibility of a PEG tube early allows the patient and caregiver ample time to make an unpressured and informed decision regarding the therapy.

**Dysautonomia.** The autonomic symptoms of MSA are individually targeted in efforts to improve quality of life and maximize overall care (i.e., untreated orthostatic hypotension would undoubtedly worsen gait disturbances and postural instability).

**Erectile Dysfunction.** Medications (such as sildenafil) may be prescribed but those with symptomatic OH must be instructed to remain supine during intercourse and for the subsequent four hours. Intracavernosal injections of papaverine or prostaglandin E1 are alternative options.

**Urinary Dysfunction.** Urinary urgency, frequency and/or incontinence with postvoid residual less than 100 mL (i.e., detrusor hyperactivity) are often treated with anticholinergics but the side effect profile of these agents may limit use, especially in the elderly. Other considerations may include mirabegron (Myrbetriq)—a beta-3 adrenergic receptor agonist, detrusor muscle botulinum toxin injections or electrical stimulation (i.e., TENS units or implanted neurostimulators). Nasal desmopressin is occasionally utilized off-label to limit nocturia and increase morning blood pressure; hyponatremia and water intoxication are potential adverse effects.

Urinary retention (i.e., postvoid residual greater than 100 mL) may necessitate intermittent self-catheterization to prevent urinary tract infection. Alpha-adrenergic antagonists are rarely used because of their potential to exacerbate OH.

**Orthostatic Hypotension.** The initial treatment of OH is non-pharmacologic:

- Discontinuation of blood-pressure lowering drugs (e.g., antihypertensive agents, diuretics, alpha-adrenergic blockers for prostatic hyperplasia)
- Avoidance of precipitating factors (e.g., sudden position changes, large meals, alcohol and heat)
- Dietary modifications, including the addition of salt to meals (10-20 g/day) and increased water and fluid intake (eight or more 8-ounce glasses per day)
- Physical activity (i.e., regular exercise—without excessive perspiration—to prevent deconditioning and performance of countermeasures, such as 30 seconds of thigh muscle contraction, when symptomatic or with prolonged standing)
- Daily application of abdominal binders and/or thigh or waist-high compression stockings

If the above are inadequate, pharmacological therapy is added. The most commonly prescribed medications are fludrocortisone (synthetic mineralocorticoid and plasma volume expander), midodrine (1-αrenoreceptor agonist), droxidopa (norepinephrine precursor) or pyridostigmine (cholinesterase inhibitor). Supine and nighttime hypertension (a potential risk primarily with the first two drugs) can be avoided by administering the last medication dose more than four hours prior to bedtime and holding if supine or sitting blood pressure is greater than 180/100 mmHg. It can also be managed with a short-acting nighttime anti-hypertensive. Electrolytes should be monitored while on fludrocortisone.

**Visual Disturbances.** Oculomotor deficits are especially challenging to treat. Zolpidem was found to improve voluntary saccadic eye movements in a small group of patients and amitriptyline reportedly affords a mild to moderate symptomatic improvement in about one-third of patients.

**Cognitive Impairment.** For prominent cognitive dysfunction and dementia, cholinesterase inhibitors and memantine are sometimes tried based on experience with these drugs in related diseases, but their role in APS is still unclear.

**Mood and Behavioral Symptoms.** Mood disturbances could include depression and/or anxiety; these may respond to one or more of the following: cognitive behavioral therapy, selective serotonin reuptake inhibitors (SSRIs) or mood-stabilizing agents. Symptoms such as apathy are often more
difficult to treat and may require lifestyle adjustments (e.g., maintaining sleep and daytime schedules, exercising regularly) rather than medication management. Psychosis (mainly visual hallucinations and/or paranoid delusions) may incite personality changes or aggressive behavior, particularly in DLB. Symptoms of psychosis are particularly challenging to treat. As dopaminergic medications can contribute, these are first adjusted if possible. Oftentimes atypical antipsychotics are then prescribed, although these drugs can exacerbate parkinsonism. Clozapine and low-dose quetiapine are least likely to worsen motor symptoms, but as clozapine can cause agranulocytosis (and therefore requires regular blood monitoring), most opt for quetiapine (despite the lack of convincing support for efficacy from randomized controlled trials). At the time of this writing, pimavanserin—a 5-HT2A receptor inverse agonist—is under review by the FDA for approval to treat PD psychosis. A final decision is expected no later than May 1, 2016.

Conclusion

Neurodegenerative atypical parkinsonisms can pose a diagnostic dilemma for clinicians and a management challenge for clinicians, patients and families. Treatment of progressive neurodegenerative disease requires a holistic approach that encompasses the patient, caregiver and entire family unit. The type and level of care will, of course, change as ongoing symptoms advance and new symptoms develop. Patients should be actively engaged in their care (e.g., shared decision-making regarding management, participation in exercise and social programs) as much as possible. If interested, they should also be offered the opportunity to contribute to research, which gives them an even more direct role in their disease and within the larger community of patients and researchers. (Available APS trials can be found on clinicaltrials.gov and soon also foxtrialfinder.org.) Caregivers play a crucial part in the management of patients with APS, and clinicians must routinely assess their levels of stress and ask about symptoms of caregiver burnout. The care team must include allied healthcare professionals and palliative care specialists as soon as deemed necessary. Physical, occupational, and speech therapists can assist at nearly every stage of the disease and social workers can supply additional resources and support, particularly with regard to in-home care services, alternative living arrangements and long-term care. Palliative care specialists can help optimize symptom management, lend emotional and spiritual support, and coordinate communication among patients, families and providers in order to align the goals and directions of current and future care.

Rachel Dolhun, MD, is a movement disorder specialist and vice president of medical communications at The Michael J. Fox Foundation for Parkinson’s Research (MJFF). Contact Dr. Dolhun at rdolhun@michaeljfox.org.

Reviewed by Irene Hegeman Richard, MD, Professor of Neurology and Psychiatry, University of Rochester.

The Michael J. Fox Foundation (www.michaeljfox.org) is the largest nonprofit funder of Parkinson’s disease research worldwide. The Foundation is dedicated to finding a cure for Parkinson’s disease through an aggressively funded research agenda and to ensuring the development of improved therapies for those living with Parkinson’s today.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
</tr>
</thead>
</table>

*For a review of DLB, see the article entitled “Dementia with Lewy Bodies: In the News and In the Clinic” in the January/February 2015 issue of Practical Neurology®, available at practicalneurology.com.
The story of alpha-synuclein and Parkinson’s disease (PD) began just two decades ago, when relatively newer genetic techniques at that time identified a single mutation in the gene encoding alpha-synuclein in a large Southern European family affected by Parkinson’s. This led to the widespread acceptance of genetics as a causative factor in PD and the observation of alpha-synuclein as a major player in the disease when it was noted to be a main component of Lewy bodies (the pathological hallmark of PD). Later, other alpha-synuclein mutations and extra copies of the alpha-synuclein gene were discovered in additional families with Parkinson’s, suggesting that several different mutations as well as gene overexpression might be linked to Parkinson’s. Although searches for alpha-synuclein gene abnormalities have been largely negative in the broad population of people with sporadic PD, research focusing on alpha-synuclein in PD remains attractive.

Our current understanding of alpha-synuclein biology is that either increased levels of wild-type alpha-synuclein protein or mutations in the alpha-synuclein gene result in abnormal folding of the protein, which in turn leads to aggregation. More recently, abnormal alpha-synuclein has been shown to move from affected to unaffected cells, suggesting an extracellular mechanism of pathological spread. These observations have led to three main avenues for alpha-synuclein-based research and development in Parkinson’s:

- Developing methods to measure and image alpha-synuclein that could lead to biomarkers, enabling earlier diagnosis and more accurate diagnoses and accelerating therapeutic development
- Blocking the production of intracellular alpha-synuclein aggregates to potentially slow disease progression
- Scavenging extracellular excess or abnormal alpha-synuclein to possibly alter disease course or even lead to improvement in existing cellular function

Potential Pathogenic Mechanisms of Alpha-Synuclein

Alpha-synuclein is found throughout the body and is ubiquitously expressed in neurons. Its precise function is unknown, but it is thought to be involved in the regulation of neurotransmitter release at the synapse. Alpha-synuclein normally maintains a soluble monomeric (unfolded) configuration but, for any number of reasons — genetic alterations, environmental toxins, cellular stresses, etc. — can misfold, aggregate into different soluble oligomeric forms and then clump into insoluble fibrils. Abnormal alpha-synuclein has been hypothesized to induce cellular toxicity through one or more mechanisms:

- Proteosome or lysosome impairment, leading to intracellular accumulation of proteins (including misfolded alpha-synuclein) that are normally degraded through this pathway,
- Mitochondrial structure or activity dysfunction, resulting in failure of cellular energy production,
Cellular membrane pore formation, allowing calcium influx that disturbs cellular homeostasis,

Generation of chronic endoplasmic reticulum dysfunction, which induces cell death, or

Interference with neuronal signaling at the synapse, negatively impacting dopamine release.\(^2,3,4,5\)

**A Theory of Alpha-Synuclein Propagation**

In addition to the above intracellular effects, some evidence supports a cell-to-cell transmission of alpha-synuclein in Parkinson’s. Braak and colleagues found pathological alpha-synuclein aggregates throughout the brain and in the periphery;\(^6\) pre-clinical PD models have demonstrated movement of alpha-synuclein between cells; and two groups independently visualized Lewy bodies in grafted fetal dopaminergic neurons of Parkinson’s patients at autopsy.\(^7,8\)

The “prion-like” hypothesis of alpha-synuclein holds that non-native forms of alpha-synuclein are released from cells into the extracellular space and taken up by neighboring cells, where they induce protein misfolding and the eventual development of Lewy bodies.\(^4,5\) Along the way, an inflammatory response, replete with microglial activation and pro-inflammatory cytokines, also may occur.\(^2,3\)

Questions remain on how alpha-synuclein pathology progresses throughout the brain and why that progression is different from patient to patient. It is important to note that while it looks like alpha-synuclein pathology can spread within the brain of the patient, there is no definitive evidence to date that PD can, either directly or indirectly, be transmitted from one person to another.\(^5\)

**Alpha-Synuclein Therapies in Clinical Testing**

Interruption of alpha-synuclein as it moves between adjacent cells is an appealing target for potential disease modification. Equally valid therapeutic pursuits include interventions at the point of post-translational modification, misfolding and aggregation. The development pipeline is rich with treatments targeting each of these missteps and several are in early stages of clinical trials:

- **A drug to inhibit formation of alpha-synuclein oligomers.**
  Neuropore Therapies, Inc. and UCB are collaborating on an oral small molecule (NPT200-11), which aims to prevent the formation of alpha-synuclein oligomers. After favorable preclinical work, the compound advanced to a Phase I clinical trial in 55 healthy control volunteers. Results demonstrated safety and tolerability of several doses.\(^9\)

- **Immunotherapies to remove aggregated alpha-synuclein.**
  The objective of immunotherapy — either passive or active — is to clear out extracellular alpha-synuclein in order to decrease or prevent cell-to-cell spread of pathology. Passive immunotherapy is the infusion of manufactured anti-alpha-synuclein monoclonal antibodies. The antibodies can be given in precise amounts and the treatment can be reduced or discontinued if adverse effects occur. But, the antibodies must be regularly administered to maintain levels and efficacy, and tolerance cannot be predicted.\(^10\)

  Active immunotherapy is analogous to immunization. In Parkinson’s, it’s the injection of a small fraction of synthetic alpha-synuclein to induce a person’s immune system to generate antibodies against it. In contrast to passive immunotherapy, it may last longer and require fewer injections over time. However, it could invoke neuroinflammation, polyclonal antibodies (which could bind off target and cause side effects), and significantly varied antibody response among subjects, namely the elderly who are less likely to generate high titers.\(^10\)

  Promising preclinical research with both types of immunotherapy supported the ongoing clinical trials.

**Passive Immunotherapy**

Prothena Biosciences Inc., in conjunction with Roche, is testing a humanized anti-alpha-synuclein antibody (PRX002). In a Phase I, randomized, double-blind, placebo-controlled, single ascending dose study of 40 healthy subjects it was shown to be safe and well tolerated and it reduced free serum total alpha-synuclein levels up to 96%.\(^11\) A second Phase I, randomized, double-blind, placebo-controlled, multiple ascending dose trial of approximately 60 PD patients has recently been completed. It assessed safety, tolerability, pharmacokinetics, immunogenicity and exploratory
biomarkers. In addition to the Prothena/Roche program, Biogen is investigating another monoclonal antibody (BIIB054) against alpha-synuclein. The Phase I randomized, double-blind, placebo-controlled, single-ascending dose trial is evaluating safety, tolerability, pharmacokinetics and immunogenicity in 66 healthy subjects and early-stage (less than five years) Parkinson’s patients.

**Active Immunotherapy**

AFFIRis AG, an Austrian biotech company, is testing an alpha-synuclein vaccine (AFFITOPE® PD01A). A Phase I safety trial, supported by The Michael J. Fox Foundation (MJFF), assessed two different vaccine doses given once a month for four months in 24 early-stage Parkinson’s patients (Hoehn & Yahr stage I/II; diagnosed within the last four years) and eight healthy controls. The vaccine was deemed safe and well tolerated, and approximately fifty percent of the patients developed alpha-synuclein antibodies in the serum and cerebrospinal fluid (CSF). A follow-up “booster” study, also funded by MJFF, evaluated the safety, tolerability, and immunological and clinical activity of one administration of two different doses of a “booster” immunization. The booster was safe and well tolerated; only injection site reactions were more common in the treatment group. Eighty-six percent (19 of 22) vaccinated patients generated an immune response; of these responders, sixty-three percent (12 of 19) produced alpha-synuclein-specific antibodies. Preliminary observations revealed that eight of the 19 responders (42%) did not require an increase in dopaminergic PD medication during the observational study period (three years on average per participant), and five of these eight (63%) had stable UPDRS III scores at study conclusion. A “reboost” study, also funded by MJFF, in which volunteers will be given a second boost vaccination, has finished recruitment. This trial will evaluate long-term safety, immunologic and clinical response; results are expected in mid-2017.

**Challenges in the Development of Alpha-Synuclein Therapies**

With so many agents moving forward simultaneously, there is reason to be hopeful about a potential alpha-synuclein-based disease-modifying therapy. Any neurological drug has a convoluted road to development, though, and alpha-synuclein-targeted therapies likely are no exception. In learning about and overcoming the hurdles related to alpha-synuclein, however, we’re getting a better understanding of the disease, and moving closer to possible disease modifying therapies and a promising biomarker.

» **Immunotherapy raises a unique set of challenges.** Antibodies are big molecules so whether they can cross the blood brain barrier in sufficient quantities to make an appreciable impact is one concern. Alzheimer’s trials, however, have proven this feat is achievable and advances in drug delivery may be able to utilize blood brain barrier receptors to shuttle antibodies across, thereby improving antibody transport. Another uncertainty relates to antibodies’ activities once they gain access to the central nervous system. Do they bind to the toxic form(s) of alpha-synuclein? And, since immunotherapy doesn’t get at intracellular alpha-synuclein, which is where the majority resides, does immunotherapy exert a sufficient effect? Future efforts may need to incorporate viral-vector-mediated and other delivery techniques to reach alpha-synuclein inside the cells.

» **The toxic species of alpha-synuclein is unclear.** Soluble oligomers are the most likely harmful conformation and, as such, are the most often targeted with current therapeutics. Still, any or all of the abnormal forms of alpha-synuclein could be the actual offender. Researchers are working to pinpoint the pathological species, and MJFF is funding a number of these endeavors.

» **Normal role(s) and levels of alpha-synuclein are unknown.** As therapies affect alpha-synuclein, it’s imperative they don’t impede normal function or reduce levels below the lower limit of normal. Great strides in understanding the protein’s physiological role have been made but its full function(s) and normal levels have not yet been elucidated. With continued trials and better quality assays, we will learn this critical information, which will help advance therapeutic development.

» **Assays of alpha-synuclein are either not available or standardized/validated.** Creating consistent measurement processes and standard values for peripheral (e.g., serum and CSF) alpha-synuclein assays will make
reporting of trial results and comparisons across them easier. Studies have demonstrated that PD patients have lower total alpha-synuclein levels in the CSF but oligomeric or pathological levels cannot yet be reliably measured. An early safety trial of passive immunotherapy measured total serum alpha-synuclein levels but the clinical significance of this is not yet known. MJFF is funding research into the validation of alpha-synuclein biofluid and tissue assays. Increasing the specificities of these tests will allow for more informative, dependable measures and more refined therapeutic approaches.

**Alpha-synuclein cannot be imaged in vivo.** Rather than using surrogate peripheral measures, it would be preferable to directly visualize alpha-synuclein load in the brain. An alpha-synuclein imaging ligand could confirm the diagnosis of Parkinson’s by assessing the presence and distribution of alpha-synuclein in the brain, ensure the right patients are enrolling in clinical trials and objectively measure therapeutic impact. An imaging agent would markedly accelerate ongoing therapeutic endeavors. To fuel these efforts, MJFF leads a collaboration of investigators called the Alpha-Synuclein Imaging Consortium and recently announced an Alpha-synuclein Imaging Prize, a $2 million award for the first team to create a selective alpha-synuclein PET tracer.

In lieu of or in addition to imaging alpha-synuclein in the brain, peripheral measurements of the protein may serve as a biomarker. Efforts are ongoing to characterize alpha-synuclein levels in various body regions (CSF, serum, colon, skin and submandibular gland) in people at all disease stages.

These hurdles are not insurmountable. They should not be viewed as deterrents to alpha-synuclein-based therapies but rather as steps that, as they are addressed, move therapeutic development and biomarker validation forward in parallel. With so many potential disease-modifying therapies in clinical testing, we are closer than ever to realizing a treatment that could alter the course of disease. For many people with Parkinson’s and their providers, this can be a source of great hope and optimism.
REFERENCES


*For a review of DLB, see the article entitled “Dementia with Lewy Bodies: In the News and In the Clinic” in the January/February 2015 issue of Practical Neurology®, available at practicalneurology.com.