Parkinson’s Disease: Current and Future Therapies Across the Stages
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Abstract
Parkinson's disease is a common neurodegenerative disorder affecting millions of people worldwide. This article discusses an introductory approach to treatment with currently available therapies from one clinician's perspective, and highlights some recent developments of interest within the preceding year.

Article
Parkinson disease (PD) affects an estimated million people in the United States alone, and projections are that the number will double by 2030. Risk increases with age, and about 1/100 of those over 60yo will develop Parkinson disease.

The cardinal motor symptoms of Parkinson disease are tremor, rigidity, bradykinesia or akinesia, and postural instability or gait changes. Particularly in early PD, but even throughout the course, not all of these features may be present, but bradykinesia is a mandatory component. Most commonly, in the first few years features are subtle and nonspecific. Decrement in size or clarity of handwriting or a “stiff shoulder” may lead to misdiagnosis until more classical features appear. Loss of facial expression (hypomimia) or vocal volume (hypophonia) and expressiveness are nearly universal at some point in the disease. The impact on gait may initially be limited to a unilateral decrease in arm swing on the more affected side. Because Parkinson commonly presents asymmetrically, friends and family may inquire about suspected stroke or injury before accurate diagnosis is made. With time, shortening of steps and less fluid turns are typical. The classical image of a Parkinsonian gait is that of stooped posture, short steps, and multi-step turns, but this may not be seen for years into the diagnosis. In advanced PD, the features of festination and freezing of gait may emerge. Festination describes an anteropulsion wherein the center of gravity propels forward, and shortened steps escalate in pace so that the person tends to lose control and “run when they try to walk.” Freezing is a disturbance particularly of gait initiation where intrinsic control of initiating movement is disrupted and the motor aspect is delayed or blocked. In walking, this translates to a patient wishing to move but feet “not listening,” or falls because the feet did not move when intended. Close spaces like closets and elevators and transitions in direction or footing seem to be particular triggers. Interestingly extrinsic cues to move such as counting, lines to step over (such as tape on the ground, a laser line from a cane, or another person's foot), or encouragement to take a big step may help break the freezing.

With treatment, many of these motor features may be improved. Gait features may be particularly refractory to oral medications, and adjunctive physical therapy is critical to incorporate, particularly with experienced therapists familiar with the motor aspects of PD. Speech and occupational therapies are also key components of maximizing quality of life and independence.

In more established to advanced PD, the therapeutic window becomes increasingly narrow. Time with satisfactory control of motor symptoms by medication may be flanked by periods of peak dose dyskinesia, abnormal involuntary movement that can affect any part of the body. This ranges from subtle swaying of the trunk which is well-tolerated to aggressive whole body movements that can make it difficult to stay seated in a chair or may impact gait. Dyskinesia may resolve during a period of optimal control of
symptoms and be followed by wearing off, during which symptoms of Parkinson disease such as stiffness, slowness, and shuffling return. Some patients may experience secondary dystonia, such as toe curling that is most common during wearing off of therapeutic benefit. Cervical dystonia and blepharospasm can also occur and may be persistent or fluctuating with dosing intervals. Maintaining the optimal “on” time can be a great challenge in advanced PD, leading to the search for more aggressive or novel therapeutic strategies.

The motor features of Parkinson disease traditionally have been considered to be the more predictable aspects, although the time course to manifesting those may be quite variable between individuals. Genetic makeup, baseline activity levels, and age at presentation may influence rate of progression. Most individuals with PD will manifest some non-motor feature over the course of the illness as well. These range from sleep and mood disorders, to gastrointestinal problems (constipation, gastroparesis, and sialorrhea) and dermatologic manifestations (seborrheic dermatitis). REM behavior disorder manifests as lack of physiologic paralysis during REM sleep, such that the individual may act out the dreams or have limb movements that disrupt sleep quality. High index of suspicion should be present when excessive daytime somnolence is reported or bed partner complains of disruptive or active sleep. Other sleep disorders such as insomnia and obstructive sleep apnea are more common as well. In one of the largest prospective clinical trials ever done in PD, the National Parkinson Foundation Quality Improvement Initiative discovered that about 61% of patients with PD have symptoms of depression, and 39% meet diagnostic criteria for minor or major depression. Unfortunately, treatment of depression is variable across treatment centers and typically inadequate. Anxiety is incredibly prevalent in PD as well, perhaps even more so in younger onset patients. This may be associated with wearing off of medication between doses, or independent. With or without depression, fatigue and apathy are common sources of distress that are difficult to resolve pharmacologically. Ruling out depression, sleep or thyroid disorders are important. Constipation and other signs of autonomic nervous system dysfunction including orthostatic hypotension, erectile dysfunction, and temperature dysregulation may occur. Pain in PD is often attributable to other physical factors such as arthritis and postural changes, but can also be associated with end of dose wearing off, especially cramping muscular pain.

Expectations for progression are often important to people seeking treatment. Parkinson has been classified into subtypes and a study with autopsy-confirmed diagnosis has revealed that the tremor-predominant subtype seems to have the most favorable prognosis. Akinetic-rigid and mixed subtypes seem to progress more rapidly. One study over a decade ago suggested that the first three years of diagnosis tend to be a “honeymoon period” of relatively easy control of symptoms. In that study motor complications arose 3-8 years into the course, followed by refractory symptoms in the 8-12 year range, and cognitive decline after 15 years of diagnosis.

Etiology of PD remains elusive. Theories range from oxidative stress and mitochondrial dysfunction, to accumulation of toxic exposures over time. A prion like transmission has been suggested based on passage of pathology into implanted grafts. A potentially unifying hypothesis is that insults of multiple types may result in ubiquitin proteasome proteolysis dysfunction and inadequate “clean up” of oxidative insults from dopamine metabolism.

Diagnosis is primarily a clinical one, supported by suggestive clinical features and course and responsiveness to levodopa. Brain imaging may be considered when vascular etiology is suspected, such as with stepwise progression or focal neurological signs. “Otherwise, when further diagnostic support is desired, multiple modalities have been used to image integrity of dopaminergic function. DaT scan is commercially available and uses ioflupane I-123 to bind presynaptic dopamine transporters using SPECT imaging. This is helpful in distinguishing essential…..or other atypical forms. Flurodopa-PET is another means of imaging dopa decarboxylase activity and dopamine turnover in the striatum. Additional approaches and tracers have been used that are less commonly employed. These include 18-FDG PET to
assess regional metabolic changes in glucose metabolism, 18-F-dihydrotetrabenazine PET to study vesicle monoamine transporter activity, transcranial sonography and diffusion tensor imaging. Imaging is not typically necessary, however.

Therapeutic options in Parkinson disease center around enhancing dopamine neurotransmission. Levodopa remains the most effective medication for Parkinson disease. It is converted by tyrosine hydroxylase and dopa decarboxylase to dopamine, and administered combined with carbidopa which inhibits the peripheral dopamine decarboxylase. This helps prevent peripheral conversion to dopamine, which causes gastrointestinal distress, and allows L-dopa to cross the blood brain barrier. Some patients may need more than the typical 25mg carbidopa, and this can be prescribed separately to overcome gastrointestinal intolerance. Levodopa is available in standard form with carbidopa (Sinemet), in orally disintegrated form (Parcopa), or combined with entacapone (Stalevo). In the U.S., continuous duodenal infusion with levodopa gel is only available within clinical trials.

Anticholinergics- (trihexyphenidyl (Artane) and benztrapine (Cogentin)- are one of the oldest treatments for PD but have a limited role primarily in early PD due to side effect profile including risk of xerostomia, urinary retention, cognitive clouding, and hallucinations. Amantadine was initially developed as an anti-influenza medication but subsequently demonstrated benefit in PD. It is most helpful in mild early PD especially for tremor, for mild fatigue, and in advanced PD to offset dyskinesia. Side effects may include lizado reticularis, disrupted sleep if taken after the late afternoon, cognitive clouding and hallucinations. Selegline (Eldepryl, Zelapar ODT) and rasagiline (Azilect), monoamine-oxidase type B inhibitors, and entacapone (Comtan, or Stalevo in combination with carbidopa/levodopa), a catechol-O-methyl transferase inhibitor, inhibit the two enzymes which metabolize dopamine, rendering greater availability at the synapse. Tolcapone is an older COMT-inhibitor which was found to have risk for fulminant hepatic failure, so has limited use with strict monitoring. MAO-B inhibitors are generally well-tolerated but raise some concern, particularly from pharmacies, for risk of serotonin syndrome when combined with SSRI’s. In practice this combination is quite common and complications are rare. Further, the tyramine restriction traditionally advised is based on the concern for inhibition of MAO-type A, which has a role in tyramine metabolism. Doses used in clinical practice have very high selectivity for MAO-B. These medications are primarily useful in early mild PD, or in hopes of extending levodopa benefit to bridge across wearing off intervals. Common side effects of COMT-inhibitors are discoloration of body fluids, diarrhea, aggravation of dyskinesia, or confusion.

Dopamine agonists pramipexole (Mirapex) and ropinirole (Re) is a once daily transdermal formulation. Potential side effects include somnolence or even sleep attacks, nausea, hypotension, dizziness, edema, and compulsive or impulsive behaviors. These can include urges to gamble, spend impulsively, and eat compulsively or to have preoccupying thoughts and urges of a sexual nature. Compulsive hobbying may occur as well, such as crafting, fishing or other diverse manifestations. Dopamine agonists need to be weaned to avoid a withdrawal syndrome. Apomorphine is a fast-onset, short-acting injectable rescue medication for sudden, unpredictable wearing off. First dose should be administered in clinic with pre-medication for nausea and close monitoring for hypotension according to protocol.

**Approach**

Initial choice of agent should not be considered to be formulaic, as individual factors and preferences may influence choice of agent and typically there is more than one reasonable option. A case-based approach highlights the need for flexibility in treatment approach, from one clinician’s perspective.

**Case 1:**
A 52 year old executive presents because of right arm tremor, change in handwriting, and stiffness of the right shoulder.

The first consideration in approaching patient management is determining which symptoms require treatment, and establishing goals relevant to individual patient's quality of life. In this young executive, even a subtle tremor was considered bothersome, and medication was desired. A reasonable consideration would be amantadine, which is most useful in mild tremor suppression, for fatigue, or later in the course for its antidyskinetic effects. MAO-B inhibitors are also great first line agents in mild early PD. Anticholinergics may be considered as well, but risks of cognitive clouding, hallucinations and somnolence need to be carefully considered particularly in advanced age patients. Of course, dopamine agonists and levodopa can be considered as first line agents, but in this case of very mild symptoms in a treatment naïve patient, it may make sense to start with lower potency agents. Levodopa should not be denied when symptoms merit quick and effective resolution, but using another agent first may help delay motor fluctuations.

**Case 2**

A 64 year old woman has had PD for 4 years, managed on selegiline monotherapy. She is beginning to experience painful cramping in the legs and her spouse feels she is beginning to shuffle. She notices a harder time keeping up with the dance moves in their recreational dance group.

This patient is having impairment of ability to partake in physical and social activities. A dopamine agonist may offer adequate potency to resolve her symptoms, with close counseling for risk of side effects (see above). Levodopa is an option as well, and may be preferred if she is at high risk of cognitive clouding or demonstrates intolerance of agonists. Anticholinergics or amantadine may be considered but may be unlikely to yield adequate therapeutic potency in this patient. The role of incorporating physical therapy is important in gait issues.

**Case 3**

A 64yo man was diagnosed with PD two years prior when he had some slowness of movement and gait changes. Within one year, he had progression of gait to the point of occasional falls and needing a cane. Over the second year, he needed a walker and shortly thereafter used a wheelchair due to frequency of falls. Levodopa gave him some vague improvement but no clear “on/off” effect.

He complained that on rising from a chair, he felt lightheaded and could nearly pass out.

This case highlights the need to constantly reconsider accuracy of the diagnosis. In the first year, PD and atypical parkinsonism may be nearly impossible to distinguish. Rapidity of progression and suboptimal levodopa response are suggestive of an alternative diagnosis. The autonomic symptoms early in the course raise question of multiple system atrophy, although these symptoms may be seen in PD as well. One should treat non-motor symptoms that impact quality of life, including orthostatic hypotension. Compressive stockings, liberalized salt intake, and agents such as midodrine, fludrocortisone, and pyridostigmine may be utilized.

**Case 4**

A 62 year old woman with 8 year history of PD on combination therapy with Mirapex tid, Stalevo q 3hr while awake, and selegiline complains of bothersome dyskinesia half an hour after Stalevo, but wearing off 20-30minutes before the next dose.
At this point, one may consider amantadine for suppression of dyskinesia, but deep brain stimulation surgery may be an option. In a levodopa-responsive, cognitively intact patient who is a good surgical candidate and without unstable psychiatric disease, DBS may help suppress dyskinesia and improve dyskinesia-free on-time.

A few interesting updates

With current therapies having obvious limitations and with the failure thus far in finding a truly neuroprotective therapy, the community is always hungry for developments to improve early diagnosis, gain insight into pathogenesis, or find new directions of treatment. The following are some interesting updates of the last year, not exhaustive, but of clinical relevance.

One of the greatest shortcomings of current PD management is that diagnosis occurs when the neurodegenerative cascade is well in progress, and interventions merely combat the consequences of that. Ultimately, the goal is to halt the process before an irreversible sequence is in place, or before destruction to the dopaminergic pathways occurs. Earlier diagnosis of at risk individuals is a critical aspect of that endeavor. Large trials are ongoing to explore blood, saliva, CSF and other biochemical parameters to distinguish early PD. One interesting finding to clinicians, while those biomarkers continue to be elucidated, is that clinical biomarkers may be helpful in distinguishing PD in early patients. The DeNovo Parkinson (DeNoPa) cohort included 159 drug naïve PD patients compared to 110 healthy controls using a number of parameters including the Non-motor symptom (NMS) Questionnaire, Scopa-AUT GI score, and Smell Identification Test. The triad of constipation, anosmia, and REM behavior disorder reached an AUC of 0.913 (95% CI 0.878-0.948) for separating PD from healthy controls. Additional values including serum cholesterol, mean heart rate, transcranial sonography of substantia nigra and polysomnography for RBD could increase the AUC to 0.963 (95% CI 0.943-0.982).

In addition to early diagnosis, identification of risk factors is one step in disease modification. Risk factor research has consistently demonstrated that caffeine use is associated with lower risk of PD. A recent metaanalysis including 13 studies, 901,764 patients for coffee; 8 articles, 344,895 for tea; 7 articles, 492,724 for caffeine, explored whether caffeine or coffee could be credited with this risk reduction. Interestingly, there was a linear dose-response relationship for lower PD risk with increased tea and caffeine consumption (smoking-adjusted risk reduction of 26% for every 2 cups/day and 17% for every 200mg/day, respectively), but protective benefit of coffee was non-linear and maximized at 3 cups/day (smoking-adjusted RR 0.72). The impact of caffeine on individuals already having PD has been looked at in a small 6 week study, 30 patients receiving caffeine and 31 placebo. The target dose of 200mg bid (roughly 3-4 cups of coffee/day) did not improve sleepiness in PD by Epworth scale, but improved total UPDRS by 4.69 points and motor subscale by 3.15 points over placebo. Blinding in such a study may be questionable, and tolerance over time may be a concern.

The evidence that caffeine reduces PD risk has led to the identification of a potential new therapeutic target, the A2A receptor. Caffeine binds the adenosine A2A receptor, which has high prevalence in the basal ganglia and co-localizes with dopamine receptors. This G protein-coupled receptor family has a role in activating adenyl cyclase and synthesis of intracellular cyclic AMP. There appears to be a role in glutamate and dopamine release. A number of therapeutic trials of A2A receptor antagonists (for example, Preladent, Tozandent (SYN115), and most recently Istradefylline), have had encouraging early results, but less robust findings in larger controlled trials. This year Mizuno et.al published findings that Istradefylline 20mg vs. 40mg vs. placebo in 373 PD fluctuators demonstrated reduced off time by (-0.99; -0.96; -0.23) in a 12 week study. Sufficient benefit to gain FDA approval could was not demonstrated but it has been approved for use in Japan.
In addition to risk factor analyses, genetic studies remain an invaluable tool for deducing etiology of PD. This year a new gene was recognized causing PARK 15, or parkinsonian pyramidal syndrome, which leads to juvenile onset Parkinsonism and spasticity. The FBXo7 (F-box only protein 7) gene encodes a protein for an ubiquitin ligase. Mutations lead to impaired targeting of proteins for degradation, and specifically inability to clear defective mitochondria. The FBXo7 protein was subsequently studied in PD, MSA, AD, & PSP. Anti-FBXo7 antibodies had widespread immunoreactivity, but no overall difference in PD vs. control. Interestingly, however, there was marked co-localization of FBXo7 activity with alpha-synuclein-positive inclusions but only weak positivity in tau-positive inclusions, maintaining the possibility that there may be a link to pathogenesis of synucleopathies.

Treatment updates

Recent studies have looked for variables to impact levodopa efficacy. Based on risk analyses suggesting nicotine users have less risk of PD, a study of transdermal nicotine followed by levodopa/benserazide (100/25) demonstrated disappointingly, decrease in levodopa absorption by 34-60% with no impact on gastric motility. Notably, this was performed on healthy subjects. Multiple studies have investigated the impact of gut bacteria on levodopa efficacy with H.pylori being the most common target of interest. This bacteria is present in more than 50% of the typical age population susceptible to PD. Prior evidence has demonstrated that treatment of H.pylori can improve on time in PD. Fasano and colleagues looked at not just H.pylori but bacterial overgrowth in general. PD may impact gut motility, raising question that bacterial population could be relevant. Glucose, lactulose, and urea breath tests for H.pylori and bacterial overgrowth, and ultrasound for gastric emptying were utilized. Small intestine overgrowth, but not H.pylori, was more common in PD, as was abnormal gastric emptying. Both infections were associated with more motor fluctuations. Small intestine overgrowth also associated with delayed on time and dose failures. Eradication with antibiotics led to improvement of motor fluctuations but relapse rate of infection at 6 months was high (43%).

Given the challenges of resolving motor fluctuations, newer formulations of levodopa remain of interest. The current carbidopa/levodopa CR formulation has slower time to onset and less predictable benefit than the immediate release form. In trials, this formulation did not reduce off time or dyskinesias, nor increase on time. A new formulation (IPX066) with beads that dissolve at variable rates in the GI tract has been studied. In a phase 3 randomised, international double-blind trial at 68 centers, onset of efficacy was similar to IR, but with longer duration of benefit (1.16 hour less off time). 393 PD fluctuators were included. Patients required 3.6 doses per day vs. 5 doses for IR.

Non-motor symptom treatment often seems to receive less attention, and constipation is a common aggravation in PD. The chloride channel activator lubiprostone (Amitiza) enhances fluid secretion in the gut and reduces gut permeability, increasing intestinal motility. In a double-blind, randomized placebo-controlled trial of 52 patients with PD, 48mcg/day led to “marked or very marked clinical global improvement in 16 of 25 (64%) subjects receiving drug versus 5 of 27 (18.5%) receiving placebo.” Constipation rating scales and stool diaries improved relative to placebo.

With the inherent problems in orally administered levodopa, continuous duodenal infusion has been considered a potential alternative to deep brain stimulation in motor fluctuators on levodopa. Recent publications regarding levodopa/carbidopa intestinal gel (LCIG) continue to support its efficacy. In 25 patients prospectively followed at an Italian center for 3 years, 17 completed the course (5 discontinued, 3 died unrelated to study). Dyskinesia (UPDRS IV) and quality of life (PDQ-39) improved, with essentially stable total levodopa dose. Cognition significantly worsened with time in 41% and tube-related side effects were very common. In a prospective open-label international 54 week study of 192 patients on LCIG
(baseline 6.7hr/day off time; average duration PD 12.4 years), there was a mean improvement in off time of 3.9hr less (+/-3.2), with mean 4.6hr more on time without troublesome dyskinesia (+/-3.5). Serious adverse effects occurred in 31.3%, with abdominal pain (31.3%) and insertional complications (21.4%) being among the most common side effects.21

Deep brain stimulation is an established effective surgical treatment, but optimal time for intervention remains unknown. The long-term outcome of subthalamic nucleus DBS in YOPD was explored in 17 patients (mean disease onset 32.3yo) followed for 7 years. UPDRS II-IV improved significantly at 7 year follow-up with low morbidity, and levodopa daily dose equivalent was reduced. Transient stimulation-induced dyskinesia occurred in 47.1%. On/off meds and on/off DBS were assessed, allowing the observation that levodopa response declined slowly over time and that DBS and medication remained synergistic. An interesting finding was that dopamine dysregulation occurred in 11.8%. The optimal time to intervene in YOPD or typical PD remains unknown, however.22

These updates are encouraging and highlight the many unmet needs of this complex disorder.
References


