Parkinson’s Disease: Pathophysiology and Medical Therapy
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Introduction

Over one million American’s suffer from PD with 60,000 new cases of Parkinson’s Disease (PD) diagnosed in the United States each year.[1, 2] The incidence of PD increases with age and is estimated at 20 per 100,000.[3, 4] PD and its associated morbidities cost society approximately 5.6 billion dollars per year.[5] Its cost in quality of life for affected individuals, however, cannot be measured. Significant advances in medical (dopamine agonists, dopamine extenders, and selective dopamine blockers) and surgical therapy (pallidotomy, deep brain stimulation (DBS), and transplant) as well as an improved understanding of physiology, genetics, pathology, and molecular biology of the disease.

History

James Parkinson was a general practitioner in the East end of London, better known for his social activities than for his descriptions of a shaking disease. He wrote revolutionary pamphlets under the pseudonym “old Hubert” and was hailed as an agitator on more than one occasion.[6, 7] His 1817 Essay on the Shaking Palsy went largely unnoticed until Charcot and others began referring to it as Parkinson’s Disease. Parkinson referenced Galen and Boetius and offered a compelling description of patients with “shaking and shuffling” which is comparable to modern textbooks and articles. Despite his erroneous assumption that PD was due to a lesion in the spinal cord, as well as his failure to recognize that the tremor abated during sleep, his description is thorough. It was evident however, that Parkinson had little understanding of Parkinson’s plus
disorders, one of which (multiple systems atrophy) served as his first case description.[6] The re-exploration of his essay has led to a revival in the study of what is now the second most common neurodegenerative disease. [4]

**Mechanisms of Disease**

The mechanisms causing PD remain a mystery. We have, however elucidated over the past several decades many risk factors, and potential causes. Oxidative stress, nitrous oxide formation, mitochondrial dysfunction, toxins, and inflammatory processes may all play a role in the pathogenesis of this disease by accelerating apoptosis of dopaminergic cells in the pars compacta portion of the substantia nigra (SNc).[3, 8-16] Additionally, it has been postulated that increased output of the excitatory neurotransmitter glutamate, may cause cell loss in the SNc by the mechanism of excitotoxicity.[10, 17, 18] Immune mediated destruction of cells by glia, may also play a role in cell loss in the SNc by accelerating the release of toxic cytokines.[19]

Oxidative stress was recognized in 1975 as a potential cause of PD. PD patients have a significant reduction in the activity of catalase and peroxidase in the striatum and substantia nigra. The reduction in peroxidase results in a decrease in production of peroxides leading to injury and death of dopaminergic neurons.[9] Also reported is an increase in superoxide dismutase activity leading to an increase in hydrogen peroxide and iron deposition. In the presence of iron, cytotoxic hydroxyl radicals are formed at an accelerated rate causing an increase in cellular destruction.[12, 20] Further support for a possible role of oxidative stress in promoting cell loss was the discovery of decreased glutathione in the substantia nigra. Glutathione is a natural anti-oxidant serving as a substrate for glutathione peroxidase. Glutathione is consumed when glutathione
peroxidase catalyzes the peroxidase reaction. Reduced glutathione is likely a marker of oxidative stress.[21, 22]

The thirty percent decrease in mitochondrial complex I activity in substantia nigra neurons has raised questions as to whether PD patients have a greater susceptibility to apoptosis or environmental influences.[23, 24] A recent rat model of Parkinson’s disease utilized the mitochondrial toxin rotenone to produce Parkinsonian animals.[25, 26] This toxin is an inhibitor of the mitochondrial respiratory chain, and is a commonly used pesticide. Its discovery has led to increased speculation as to the role of environmental toxins in PD.

The most important description of a model of parkinsonism is that of Langston. Parkinsonian symptoms were induced by L-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a contaminant of synthetic heroin first seen by Langston in California after several recreational drug users presented with parkinsonism, suggesting that environmental toxins could precipitate symptoms. This discovery subsequently led to the development of the primate MPTP model of PD. MPTP is converted to MPP+ by monoaminoxidase-B (MAO-B). MPP+, the mitochondrial complex I inhibitor, is concentrated in dopaminergic cells as a result of the dopamine reuptake system. MPP+ is selectively toxic to the nigral-striatal pathway and produces motor deficits similar to PD in humans and non-human primates. Patients respond to antiparkinson medications, and may develop dyskinesias and dystonia. Pathologically Lewy Bodies are not seen, though in older primates there may be similar inclusions. The MPTP model of PD has been highly useful in the study of PD,[27] and the pathophysiologic mechanisms underlying its development.[28, 29].
Other environmental factors including rural living, well water use, exposure to pesticides, exposure to industrial chemicals, manganese toxicity (miners), and dopamine blocking drugs have also been implicated as potential risk factors for PD.[1, 2, 30]

**Genetics**

Important advances have been made in the understanding of genetics in PD in part due to the historical observation of Gowers who noticed an increased incidence within certain families.[4, 31] Both an autosomal dominant trait with variable penetrance and multifactorial causation have been identified.[4, 17] Four mutations (Park1-4) have been described in families with symptoms of PD. Two of the mutations (Park1 and Park3) were found in genes coding for alpha-synuclein, a component in Lewy bodies. The role of alpha-synuclein, an enzyme involved in ubiquitin metabolism, is unknown, but it may contribute to aggregations that increase the selective vulnerability of dopaminergic neurons to oxidative stress.[32, 33] Additional genetic information has been derived from the observation that possessing the apoprotein E4 allele (Alzheimer’s allele) as well as an alpha-synuclein allele may impart an increased incidence for developing PD.[32, 34, 35]

**Physiology of PD**

An understanding of neuroanatomy and physiology of the basal ganglia and its related structures has allowed us to develop a model of its functional organization (Figure 1). The model views the basal ganglia as part of a family segregated circuits involving the thalamus and cerebral cortex.[36, 37] These circuits originate from different areas of the cerebral cortex and project to specific portions of the basal ganglia. These structures in turn project to different regions of thalamus and return to their site of origins in the
frontal cortex. Both motor and nonmotor circuits have been described. Nonmotor circuits project to association and limbic areas, while the motor circuits project to areas of the cerebral cortex involved in the control of movement. The “motor” circuit has been considered the most important in the pathogenesis of PD as well as other hypo and hyperkinetic movement disorders. Many of the non-motor circuits in PD play central roles in the behavioral and non-motor symptoms of disease.

The motor circuit originates in the pre-central motor and somatosensory cortical areas and projects to motor areas of the basal ganglia and thalamus en route to its return to motor and premotor cortical areas. Cortical input influences the two major output routes of the basal ganglia, the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr), through two pathways. The routes are referred to as the direct and indirect pathways. The direct pathway (D1 receptors) takes origin from putaminal medium spiny neurons and contains monosynaptic connections to GPi and SNr. The indirect pathway (D2 receptors) originates from medium spiny neurons and projects via the external segment of the globus pallidus (GPe) and subthalamic nucleus to the GPi and SNr. There are also return projections from the STN to GPe, and direct projections from GPe to GPi, SNr, and the reticularis nucleus of the thalamus.[38] A simplified version of this model is presented in figure 1.

The pallidal receiving area of the GPi projects to the motor thalamus, which consists of ventralis lateralis pars oralis, VLo and ventralis anterior, VA.[39-41] VLo and VA project predominantly to premotor and supplementary motor areas, but also have smaller projections to primary motor and arcuate premotor areas.[42-44] The SNr projects to ventralis anterior magnocellularis, VAmc, which in turn projects directly to
the prefrontal cortex.[45] GPi and SNr also project to the superior colliculus and midbrain tegmentum[46, 47], and may account for some of the eye movement abnormalities present in PD patients.

The intrinsic and output projections from the basal ganglia (putamen, GPe, GPi, SNr) are all gabaergic and inhibitory with the exception of the STN which is glutaminergic and excitatory. The projections from the cerebral cortex to the putamen as well as the projections of thalamus to cortex are glutaminergic and excitatory.

The basal ganglia thalamocortical circuit in the parkinsonian monkey has led to a model useful for understanding the changes seen in PD. Loss of dopamine cells in SNc leads to differential changes in neuronal activity in the direct and indirect pathways. In the direct pathway there is a decrease in inhibitory activity from the putamen to the GPi, leading in an increase in inhibitory activity of GPi to thalamus and brainstem. In the indirect pathway there is a loss of excitation of the GPe by putamen resulting in decreased inhibitory output from GPe to STN. This decreased inhibitory output leads to excessive excitatory output to the GPi, increasing inhibitory output of GPi to the thalamus and brainstem. Thus, both the direct and indirect pathways lead to increased inhibitory activity from GPi to the thalamus and brainstem in PD.[29, 36, 37, 48, 49]

Inhibition of thalamocortical and the midbrain projections in the motor circuit has been proposed as the primary cause for the development of parkinsonian motor signs and hypokinetic features of PD.[37] The model predicts that loss or lowering of inhibitory input from the GPi to thalamus results in the hyperkinetic movements associated with drug induced dyskinesias.[50, 51] Studies of changes in mean firing rates in both humans with PD and animal models of PD are consistent with those predicted by the “rate”
PET studies in PD also support the model showing increased activity in cortical motor areas following pallidotomy consistent with disinhibition of thalamocortical pathways.[55, 56]

The observed effects of lesioning different structures in the circuit both support and refute the model. Lesions of STN and GPi improve the major motor symptoms of PD, while lesions of the GPe worsen them.[57, 58] However, lesions in the motor thalamus do not exacerbate or induce PD, but can improve tremor and rigidity.[51, 59] Lesions in GPi which are predicted by the model to exacerbate levodopa induced dyskinesias are highly effective in alleviating them in PD. Changes in the firing rate of neurons within the pallido-thalamic circuit cannot account for these observations. As a result of these observations, together with a review of the patterns of neuronal activity in the GPi, STN, and thalamus in patient and animal models of PD it has been hypothesized that the motor signs occur as a result of a combination of changes in both the rate and pattern of neuronal activity.[60, 61] More recently, alternative pathways as well as changes in the somatosensory responsiveness and amount of synchronization of neuronal activity in the pallido-thalamocortical circuit have been incorporated into the model.[62]

Other potentially important pathways in the pathogenesis of parkinsonian signs include those from GPi and SNr to the midbrain extrapyramidal area (MEA) and the pedunculopontine nucleus (PPN). The MEA sends projections back to the GPi and SNr as well as the brainstem and spinal cord, while the PPN has extensive projections to thalamus and spinal cord.[63-66]
Pathology of PD

Gross examination of the midbrain in PD reveals the hallmark loss of dopaminergic cells of the substantia nigra. Microscopic examination reveals loss of neuromelanin and accompanying gliosis in the SNc. These changes are widespread and occurring in both motor and nonmotor portions of the basal ganglia.[67, 68] Involvement of the PPN, may account for some of the axial symptoms observed in PD patients, including balance and gait symptoms.[64, 66, 69]

Intracellular eosinophilic inclusions termed Lewy Bodies may be seen in nigral neurons as well as in cortex, subcortical locations, and peripheral ganglia. They are present in 75% of cases and are considered the pathological hallmark of PD. They stain positively for ubiquitin and alpha-synuclein. The significance of the phosphorylated neurofilamentous inclusions in PD remain a mystery. Also a mystery is that they may be present in other neurodegenerative diseases including Alzheimer’s, progressive supranuclear palsy, prion disease, and diffuse Lewy body disease.[70-72]

The presence of alpha-synuclein in Parkinson’s Disease and multiple systems atrophy is useful for pathological diagnosis. Progressive supranuclear palsy, Alzheimer’s Disease, and corticobasal ganglionic degeneration do not stain for alpha synuclein, but do stain for another neural protein, tau. These staining attributes have led some investigators to refer to PD as a synucleinopathy, whereas the other diseases may be referred to as tauopathies.[71-73] This new terminology is not in wide use.

Clinical Presentation

The cardinal motor signs of PD are tremor, bradykinesia, rigidity, and a gait disorder. Patients can present in a variety of ways but often are seen first with tremor,
decreased arm swing, or shuffling gait. It is important to consider that younger patients will commonly present with pain (secondary to dystonia) and rigidity.[74] Twenty percent or more of patients with PD will not manifest tremor.[1, 68, 75, 76]

Recently diagnostic criteria have been proposed for PD.[1, 5, 77] Patients may present with one of three different phenotypic forms of disease (tremor predominant, akinetic rigid, postural instability/gait problems). Criteria for diagnosis of PD include a year or more of tremor, bradykinesia, or rigidity. Also part of inclusion criteria was responsiveness to L-Dopa therapy (at least one gram/day for a month). Exclusion criteria included abrupt onset, remitting course, stepwise progression, neuroleptic therapy within a year, exposure to toxins, encephalitis, oculogyric crises, supranuclear gaze palsy, cerebellar signs, lower motor neuron signs, pyramidal signs, severe autonomic failure, dementia at onset, early falling, cerebrovascular disease, or unilateral dystonia with apraxia or cortical sensory loss.[5, 76, 77] Presence of any exclusion criteria suggests an alternative diagnosis. Exclusion criteria may be present concomitant with a diagnosis of PD if the symptoms are explainable (e.g. the PD patient with an unrelated neuropathy, or previous traumatic brain injury). Care must be taken by the practitioner to identify exposure to dopamine blocking medications, environmental factors, genetic influences, and in differentiating PD from Parkinson’s like syndromes. There are important diagnostic clues that may be helpful in separating out these syndromes (Table 1). If the symptoms cannot be clearly differentiated, a fluorodeoxyglucose positron emission tomography scan (FDG-PET) may be helpful in discerning PD from PD plus disorders. PD usually shows a characteristic striatal hypermetabolic pattern, while the atypical Parkinson’s like disorders reveal a hypometabolic pattern.[78, 79]
The classical picture of a patient with advanced PD includes a stooped posture and a shuffling gait. The patient may have start hesitation when walking, and may freeze. Turning is often difficult and requires many steps (pedestal turning, or en bloq turning). The PD patient may have difficulty initiating gait (start hesitation) followed by a gradual acceleration with many short shuffling steps and a reduced stride length. This phenomenon where the PD patient appears to be chasing his or her center of gravity is referred to as festination.

Tremor in PD is common and is often a diagnostic feature. Resting tremor is particularly helpful in differentiating this disorder from Parkinson like syndromes or from Wilson’s Disease, Multiple Sclerosis, Holmes tremor, and dystonic tremor. Identifying tremor in PD is relatively straightforward. It is usually course and variable in amplitude with a frequency of 4-6 Hz. In some cases it may be more rapid and in severe cases it may be present during both posture and action. PD tremor is typically distal involving one or more fingers or toes. However, it may occur proximally, involving the forearm or the proximal lower extremity. It may be present locally in 1 or all 4 extremities, and may include the jaw.[68] It is not uncommon for patients to present with a slight postural action tremor, but if found on exam it requires an intensive search for an alternative diagnosis because essential tremor (ET) frequently coexists with PD. Additionally families have been described with both PD/ET or with some family member suffering exclusively from PD while others suffer exclusively from ET.[80-82] We have found that many patients referred to us with a diagnosis of PD actually have postural/action tremor in the absence of rigidity, resting tremor, or gait difficulties. Closer scrutiny and longer followup has proven many of these cases are ET.
Rigidity is also a common symptom of PD and is present in virtually all patients with more than mild disease. It is usually asymmetric and worse on the side where symptoms began. The classical pattern of rigidity can be picked up on examination by moving the wrists, elbows, ankles, and knees slowly through a passive range of motion. Patients typically exhibit a cogwheeling rigidity, which can sometimes be reinforced by having them open and close the contralateral hand while the examination of the ipsilateral side proceeds.

Bradykinesia is another cardinal motor symptom of Parkinson’s Disease. Examination reveals slow finger or foot tapping that is usually asymmetric. Patients may begin with an excellent performance, but persistence of tasks will result in fatigue, decreased amplitude of movement, and worsening dextery. In addition to tapping, and rapid alternating movements, proximal movements and truncal movements may also be slowed.

One of the first symptoms a patient may notice is sloppiness of handwriting. Gradually this may evolve into the formation of small letters when writing, a finding referred to as micrographia. If the examiner has the patient continue to write the same phrase over and over he or she may be able to demonstrate micrographia by fatiguing the patient.

Later in the disease patients may experience progressive gait difficulties and postural instability leading to a tendency to fall. The gait symptoms may have an excellent response to dopaminergic or dopamine agonist therapy, but may become more difficult to treat later in the illness if postural reflexes are lost. Falls are responsible for much of the morbidity and mortality associated with PD making the advent of physical
therapy, education, and assistive walking devices essential to the multidisciplinary approach to caring for these patients.[83]

The voice in PD has a tendency to become softer during disease progression. This finding, known as hypophonia, may occur without the patient being aware that others perceive his or her voice to be soft. Treatment of this complication is centered on optimizing medications, teaching the patient to project his or her voice (Lee Silverberg technique), and using a speech therapist familiar with PD patients.[84, 85] Later in the illness the speech may become soft and slurred making it extremely difficult to understand.

Depression in PD is common and is reported in 25-40% of all cases.[86-89] Patients complain of decreased energy, and a lack of enjoyment in their activities with or without emotional lability. These symptoms generally respond to treatment with antidepressant medications.[5, 90] Thyroid function should be checked in light of recent data that suggests an increased incidence of thyroid disease in PD.[91-96] A thyroidopathy or other endocrinopathy may prohibit optimal treatment of depression with an serotonin reuptake inhibitor (SSRI) or a tricyclic antidepressant (TCA).[96]

**Medical Therapy of Parkinson’s Disease**

The main treatment objective in administering medications to patients with PD is to improve the quality of life. In addition to many useful medications it is important to encourage a daily stretching routine and exercise program, which will improve flexibility and mobility and may decrease the need in some patients for pharmacotherapy.[5] The individual problems with the motor system encountered in PD can be treated medically depending on the situation. The mainstays of therapy include sinemet
(carbidopa/levodopa), dopamine agonists, COMT inhibitors, anticholinergics, MAO inhibitors, and amantadine (Tables 2,3). The decision to begin medical therapy is often difficult. It requires a discussion between the physician and the patient to ascertain how much the symptoms are disrupting the patient’s quality of life or ability to function at work. A slight tremor, for example, may not bother one patient, but may be embarrassing or disabling to another. Falling, severe bradykinesia, severe rigidity or pain may be an immediate indication to start medical therapy. When at the beginning of the illness there should be consideration of medicines that may be neuroprotective such as MAO-B inhibitors, or vitamin E. To date there is no conclusive study showing any medicine is neuroprotective,[97] so in our practice we educate the patient and work together in making the decision to start medical treatment.

The treatment algorithm for PD has recently changed with the advent of dopamine agonists and an understanding that beginning therapy with dopamine agonists may reduce the incidence of drug induced dyskinesias or at the least delay their onset.[5, 98] Patients who can tolerate the dopamine agonist drugs are started on these agents first and titrated to an effective dose. Sinemet (carbidopa/levodopa) is then added later in the course of the disease. This strategy has been recently shown to reduce motor fluctuations as well as levodopa induced dyskinesias.[99] Either dopamine agonist monotherapy titrated to an effective dose, or agonist therapy with the addition of Sinemet or Sinemet CR is acceptable. It is important to note that the CR preparation only delivers 75-80% of the same dose of dopamine as the regular release preparation, and may worsen motor fluctuations, levodopa induced dyskinesias, and dystonia later in the illness. Some patients, particularly the elderly who are falling may do better with Sinemet monotherapy
initially, which is generally more efficacious, acts more quickly to relieve symptoms, and may be easier to manage.

**Carbidopa/Levodopa.** Also known as Sinemet, carbidopa/levodopa is a combination of the dopamine decarboxylase inhibitor carbidopa, and levodopa. It is available as a short acting preparation as 10/100, 25/100, 25/250 tablets and as a long acting preparation known as Sinemet CR which may come as 25/100 or 50/200 tablets. When using Sinemet one should use the smallest dose necessary to control symptoms, in order to minimize potential fluctuations and LIDS. The strategy we use in our practice is to start with the 25/100 tablets (regular release) and use $\frac{1}{2}$ of a tablet two to three times a day titrating up as needed. Most patients will need at least 300-400 mg of levodopa, particularly early in the disease although there are great variations between individuals. Nausea may complicate a patient’s attempt to get on dopaminergic therapy. The addition of extra carbidopa (Lodosyn), which is a peripheral dopamine decarboxylase inhibitor, or ginger (ginger root, gingerale) may lessen or eliminate this phenomenon. In early PD, medications may be taken with food to lessen nausea, but as the disease progresses it may become important to take them on an empty stomach to ensure a regular absorption rate, and consideration should be given to reducing protein in the diet which can also slow the absorption of Sinemet.

When patients experience motor fluctuations, dystonia, or dyskinesia different strategies should be employed to treat each of these individual problems. (Tables 2,3) In general, patients who are wearing off prior to their next dose may benefit from moving dosing intervals closer together, and by adding additional doses of medication. Individual dosages may need to be decreased to lessen dyskinesia.
Dopamine Agonists. Adding a dopamine agonist as early as possible in PD is now the treatment of choice in order to lessen long term complications of domaminergic therapy.[99] Most patients will need to add Sinemet later in the course of the disease. When beginning dopamine agonist therapy one may choose from pergolide (Permax), bromocriptine (Parlodel), pramipexole (Mirapex), and ropinerole (Requip). With the exception of Parlodel, which may be less effective, the other agonists all have similar efficacies and similar mechanisms of action with the exception that pergolide has D1 and D2 agonist properties, and the others are more D2, D3 agonists. If one preparation does not provide adequate benefits or introduces unacceptable side effects, we will switch to another. The most important principle in using a dopamine agonist is to start at low doses and titrate upward slowly. Pergolide may be started at a dose of .05mg a day and titrated slowly to a dose of 1mg three times a day or higher. Mirapex is started at .125mg and titrated to 1.5mg three or more times a day, and ropinerole is started at .25 mg a day and titrated to a maximum of 24mg/day in 3 or more divided doses. Bromocriptine, an older ergot derivative medication (the others are nonergot derivatives), may be started at 2.5 mg twice a day and titrated to at least 5mg three times a day, but often titrations to 20-30 mg/day are required. These medications may be given more than two or three times a day later in the illness. The doses may need to be reduced if patients experience nausea, dyskinesia, hallucinations, sleep attacks, or other complications of therapy.

COMT Inhibitors. Two enzymes, monoamine oxidase B and catechol-o-methyltransferase metabolize dopamine. By blocking or preventing the metabolism of dopamine either of these compounds may extend its duration of action and alleviate the wearing off phenomenon in PD. COMT inhibitors, more than MAO-B inhibitors are
very useful for preventing wearing off phenomenon and sometimes in diminishing
dyskinesia, if the levodopa dose can be decreased after initiation of therapy (otherwise it
may induce dyskinesia). There are two COMT inhibitors on the market, tolcapone or Tasmart, and entacapone, or Comtan. Although more efficacious, the use of Tolcapone
(100mg two to three times a day) has been limited as a result of a few cases of liver
failure. If tolcapone is utilized, liver enzymes need to be monitored every 2-4 weeks.
The less efficacious, but safer entacapone can be particularly helpful in treating the
wearing off phenomenon. Entacapone is started at a dose of 200mg and taken one to six
times a day. It must be taken with Sinemet, as it has no effect when taken in
monotherapy. Entacapone may induce dyskinesia within 24-48 hours of initiating
therapy, and treatment of the dyskinesia should be directed at immediately decreasing the
dose of Sinemet by 10-30%. Some physicians advocate decreasing Sinemet doses
concomitant with starting entacapone therapy. Patients need to be warned that a harmless
metabolite of entacapone may cause an orange discoloration of the urine.

**Amantadine.** The multiple mechanisms of action of amantadine make it a
potentially useful drug for treatment of many of the symptoms of PD. Originally used as
an antiviral in the treatment of flu, amantadine is also a partial dopamine agonist,
decreases dopamine reuptake, is anticholinergic, and has some antiglutamatergic
properties.[100, 101] There are ongoing studies to determine if amantadine has
neuroprotective properties. Presumably through its antiglutamatergic properties
amantadine can be a powerful anti-dyskinesia medication as well as potentially helpful in
the treatment of motor fluctuations. Amantadine can be used early in PD for the
treatment of mild PD symptoms prior to levodopa therapy, or late in the disease to treat
dyskinesia. The dose ranges are 100mg one to four times a day. Practitioners should be cautious with amantadine as it may cause rash (livido reticularis), or hallucinations. Smaller doses can be administered through a liquid preparation. When complications are encountered with this medication, the dose should be reduced or the medicine discontinued.

**Anticholinergics.** The use of anticholinergic drugs may have significant benefits in tremor, bradykinesia, and rigidity in some patients, but its most striking effect is its benefit on tremor. Young patients presenting with only tremor, may benefit from a trial of one of many anticholinergic medications. Caution should be exercised as escalating doses may cause mental confusion, blurred vision, dry mouth, urinary retention, and memory disturbances. These medications should be used cautiously in the elderly. We have found that ethopropazine hydrochloride (Parsitan) is the easiest to tolerate. We generally start patients at 25mg once or twice a day and titrate slowly over many weeks to benefit and/or side effects. Trihexyphenidyl (Artane) and benztropine mesylate (Cogentin) may also be tried. A small dose before bedtime of the anticholinergic tolterodine (Detrol) may be useful for patients with urinary urgency that severely disrupts their sleep cycle.

**Antipsychotics.** Patients with PD are thought to be prone to hallucinations and psychosis because of degenerative changes in the cortex, and cross stimulation of D2, D3, and D4 receptors by dopaminergic drugs.[102] Hallucinations should be treated only if they are bothersome or disruptive to the patient. Care should be taken to reduce medication dosages when possible. The addition of selective (D3,D4) dopamine blockers such as Quetiapine (Seroquel) have added an important dimension to treatment of PD.
Selective dopamine blockers may allow higher doses of levodopa needed for symptomatic treatment of PD, while blocking receptors responsible for the development of hallucinations and other behavioral manifestations. Quetiapine is the easiest to administer and is usually the first line of therapy. It has the added benefit of increasing the amount of restful sleep. Clozapine (Clozaril) is the most efficacious drug, but its use is limited by weekly screening of the white blood cell count for agranulocytosis. Olanzapine (Zyprexa), risperadone (Risperdal), and other atypical antipsychotics may not be effective and may worsen PD motor symptoms. Neuroleptics such as haloperidol (Haldol) are contraindicated in PD because of their nonselective action on dopamine receptors.

**Antidepressants.** Patients with PD experience a high rate of depression (25-40%).\[86, 103\] Adequate treatment may be as simple as dopamine replacement or dopamine agonist therapy. We have found rates of depression in patients with PD approach 50% and may be significantly higher in later stages of disease. Treatment with any of the serotonin reuptake inhibitors, tricyclic antidepressants, stimulants, or other novel antidepressants may quickly improve energy and quality of life.\[103-105\] Patients should be considered for antidepressant therapy who relay a history of decreased energy or decreased enjoyment in life.

**Treatment of Pain, Dystonia, and Sensory Disturbances.** Some PD patients may present with complaints of pain or a sensory disturbance. Often patients will note a numbness, tingling, or pain on the side of their initial symptoms. This may lead to orthopedic procedures without improvement. The pain and sensory symptoms in PD are usually associated with the off drug state and can be improved by adding or increasing
dopamine or dopamine agonists. The PD patient with unexplainable pain should not be labeled as “drug-seeking.” If adjustment in medications does not alleviate symptoms the patient may require anti-inflammatories, muscle relaxants, and/or narcotics.

**Treatment of Postural Hypotension and Sialorrhea.** If hydration or high leg stockings are ineffective in treatment of postural hypotension (symptomatic dizziness or lightheadedness especially when standing) the administration of an alpha agonist (midodrine or florinef) should be employed. Patients should be asked to drink 6-8 glasses of water a day in order to stay well hydrated, improve gait, treat orthostatic symptoms, and combat constipation. Patients may also complain of drooling or excessive salivation. This condition is usually not due to autonomic failure, but rather to a decrease in swallowing. This can be treated with mild anticholinergics (e.g. levsin), dopamine, dopamine agonists, amantadine, and/or patient education.[1, 68]

**Treatment of Dystonia.** Pain may be due to dystonia. It most often appears late in the course of disease during “off” drug states. It is important to keep in mind that young-onset patients often present with dystonia. Dystonia, which is an abnormal contraction of agonist and antagonist muscles leading to discomfort, pain, and abnormal postures may occur at rest, but is usually worsened with movement. It may overflow to involve other body parts. Treatment is with dopamine or dopamine agonist drugs. Although dystonia is more common in the off state, it may also occur on dopaminergic therapy. In such cases a lowering of the dose of medication or altering the dosing schedule may be necessary to alleviate this symptom. In most cases of PD, it occurs most commonly in the early morning when the patient may awaken in pain because medications have worn off overnight.[5, 68, 106]
Treatment of Sleep. Common among patients with PD is REM behavioral disorder (RBD), which consists of the combination of vivid dreaming, and the acting out of dreams. This problem can be treated effectively with a low bedtime dose of clonazepam (Klonopin) or other benzodiazepines titrated to efficacy. Restless legs and periodic limb movements of sleep can be treated with dopamine agonists, dopamine, benzodiazepines, gabapentin (Neurontin), or analgesics. The PD patient who has fragmentation of the sleep-wake cycle, and sleep disturbances that are not easily treated by medications should be referred to a sleep specialist for a sleep study.

Surgical Therapies for PD

When motor symptoms can no longer be controlled by medication patients should be considered as possible surgical candidates.[68, 107-109] A rigorous screening process (Table 4) should be undertaken including a confirmation of the diagnosis, and most importantly documentation of a good response to levodopa, since this is a good prognostic indicator for patients considering surgery.[68, 107, 108] Although there are some exceptions, notably tremor, if a patient’s symptoms do not respond to medical therapy they are unlikely to respond to surgery. Frail elderly patients who are late in the course of the disease with significant comorbidities are not considered good surgical candidates. Patients with cognitive dysfunction also tend to do poorly with surgery. Surgical options include ablative procedures (thalamotomy, pallidotomy, subthalamotomy), and deep brain stimulation (DBS) (thalamic, pallidal, subthalamic). Neural transplantation remains experimental and is only available at this time for patients participating in clinical trials. Initial trials to replace dopaminergic neurons with autologous adrenal transplants benefited some patients but did not offer enough
improvement for the procedure to become routine.[110-112] Fetal cell transplants in humans resulted in improved bradykinesia and rigidity without an effect on tremor and freezing. Some patients developed severe and extremely difficult to treat “runaway” dyskinesias, even off medications.[113, 114] Clinical trials for transplant in PD currently include patients with advanced disease. Future studies may involve gene therapy using trophic factors such as nerve growth factor (NGF) to promote repair and sprouting of nigral neurons. Also, there will likely be transplantation of different dopaminergic producing cells, tissues, or stem cells to replace lost dopaminergic neurons in the substantia nigra. These studies are in the early stages of development, and whether or not they will prove effective in treating PD remains to be demonstrated.

**Thalamotomy**

Thalamotomy although effective for ET and PD tremor is no longer considered a first line surgical option for the treatment of PD. Thalamic lesions have not been demonstrated effective for bradykinesia, freezing, postural instability, or gait disorders seen in PD.[115, 116] Thalamic lesions placed in the cerebellar receiving area, the ventralis intermedius (Vim) nucleus are effective in alleviating parkinsonian tremor.[68, 115, 117] If the lesion is extended more anteriorly to include the basal ganglia receiving areas, ventralis oralis posterior, and ventralis oralis anterior (Vop and Voa), it may improve rigidity and levodopa induced dyskinesias. Bilateral thalamotomy is not generally recommended because of the unacceptably high incidence of speech problems including aphasia, dysarthria, and hypophonia.[118-121] The incidence of speech deficits associated with bilateral thalamotomy has been reported to vary from 30-50%.[118-121]
**Pallidotomy**

Pallidotomy is effective for all the major motor manifestations of PD including tremor, bradykinesia, rigidity, motor fluctuations, levodopa induced dyskinesias, and dystonia.[69, 122-124] Benefit to axial symptoms including gait, balance, and freezing problems, following unilateral pallidotomy has been less consistent and may wane over months to years. Although some patients axial symptoms may show long term benefit following unilateral pallidotomy, consistent benefit for axial symptoms likely requires a bilateral procedure. Bilateral pallidotomy, however has been associated with a high risk of hypophonia[107, 125-128], therefore DBS of the GPi or STN should be used on the side contralateral to the pallidotomy. Cognitive changes following pallidotomy have occurred when lesions encroach into the anteromedial nonmotor portions of GPi. The effects of such lesions may be significant in some cases.[123, 124, 129-131]

Two common reasons for failure of patients to improve following pallidotomy include 1) misdiagnosis (idiopathic PD is not present), or 2) lesions are placed outside of sensorimotor GPi. A patient with a partial or transient benefit, may only have a partial lesion of the sensorimotor GPi. Lesion location in sensorimotor GPi has been shown to correlate with improvement in clinical symptoms.[68, 123, 132] Alternative approaches with the gamma knife for PD have led to a high incidence of side effects due to a combination of problems with patient selection, targeting difficulties and delayed complications due to radiation effects.[133]

**Deep Brain Stimulation**

Deep brain stimulation (DBS) with implantable electrodes is a newer procedure often used in place of or in conjunction with ablative procedures. Activation of the
electrodes is achieved by an implantable programmable pulse generator that is placed below the clavicle. The pulse generator is connected to the DBS electrode by an attachment wire that travels across the posterior aspect of the neck and skull.

The mechanism of DBS remains unknown. DBS may act by reversibly suppressing or normalizing neuronal activity through the activation of inhibitory interneurons. Alternatively, depolarization block, interruption of bursting, or normalizing irregular and abnormally bursting patterns may all serve as possible mechanisms.[109, 134-136] Three targets are in use for the treatment of PD with DBS (VIM nucleus of the thalamus, globus pallidus internal segment, and subthalamic nucleus). The procedure is costly, and there are risks including lead fractures, infections, premature battery failure, and the need for frequent reprogramming.[137, 138] Advantages of the DBS system include the ability to perform bilateral procedures without speech side effects, reversible effects of stimulation, and the ability to optimize the stimulation parameters for increased benefit.

Thalamic DBS is now FDA approved for tremor in the United States. Thalamic DBS, like thalamotomy is effective in the treatment of PD tremor, but since additional motor symptoms are not treated effectively, GPi or STN DBS, should be employed. Procedures can be performed staged or simultaneously. Axial symptometology including gait usually require a bilateral procedure.[109, 139] Although STN DBS has been advocated for midline symptoms and GPi DBS for dyskinesias,[109, 140] both procedures are effective in treating the cardinal motor signs of PD and both may allow reduction of dosing of antiparkinson medications (Vitek, unpublished observations).[141, 142] Some groups have also advocated the dosages may be reduced more with STN
stimulation than GPi stimulation, and that STN stimulation provides greater improvement in motor symptoms compared to GPi, however there is little data to support this argument.[109, 140] In the only study to date that has reanonymized patients to one state or the other results were comparable.[143] Further studies are needed to corroborate this observation, and to determine the potential advantages of one site over another.

**Future Directions**

As our knowledge of the pathophysiology, genetics, and molecular biology of PD expand future directions for treatment will include new and better medical compounds, improved surgical and transplantation techniques, neuroprotection, and perhaps new technologies such as gene therapy and the use of stem cells to restore function. Familiarity of the current treatment options and research directions in PD is important for all physicians encountering these patients in order to optimize their care, increase quality of life, and to continue to provide new hope for the future.
Figure 1.

GPe = globus pallidus, external segment; SNc = substantia nigra, pars compacta; TH = Thalamus; VLo = ventrolateral nucleus; STN = subthalamic nucleus; GPi = globus pallidus, internal segment; SNr = substantia nigra, pars reticulata; Rt= Reticular thalamic nucleus.
<table>
<thead>
<tr>
<th>Syndrome:</th>
<th>Clues to Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticobasal Degeneration</td>
<td>Ideomotor apraxia, cortical sensory loss, dementia</td>
</tr>
<tr>
<td>Lewy Body Disease</td>
<td>Early hallucinations, dementia, paradoxic</td>
</tr>
<tr>
<td></td>
<td>worsening with medications</td>
</tr>
<tr>
<td>Progressive Supranuclear Palsy</td>
<td>Vertical gaze palsy, early gait and balance problems,</td>
</tr>
<tr>
<td></td>
<td>axial rigidity, dementia</td>
</tr>
<tr>
<td>Multiple Systems Atrophy (including</td>
<td>Severe autonomic disturbance,</td>
</tr>
<tr>
<td>OPCA(^1), SDS(^2), SND(^3))</td>
<td>orthostatic hypotension, cerebellar signs, postural</td>
</tr>
<tr>
<td></td>
<td>action tremor only</td>
</tr>
</tbody>
</table>

\(^1\) OPCA- olivopontocerebellar atrophy  
\(^2\) SDS- Shy Drager Syndrome 
\(^3\) SND- Striatonigral Degeneration
## Motor Fluctuations in PD

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Possible Strategies to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of Dose Wearing Off</td>
<td>Alter dosing schedule (move levodopa/agonist doses closer)</td>
</tr>
<tr>
<td></td>
<td>Sustained release preparation (CR)</td>
</tr>
<tr>
<td></td>
<td>Addition of an agonist or levodopa</td>
</tr>
<tr>
<td></td>
<td>Addition of a COMT, (Entacapone)</td>
</tr>
<tr>
<td>Freezing</td>
<td>Increase levodopa or agonist</td>
</tr>
<tr>
<td></td>
<td>Rare case of “on” freezing may need to reduce levodopa</td>
</tr>
<tr>
<td></td>
<td>Use dopamine agonists in addition to levodopa</td>
</tr>
<tr>
<td></td>
<td>Have patient count out loud/march in place</td>
</tr>
<tr>
<td></td>
<td>Visual cues: laser pointer, inverted cane</td>
</tr>
<tr>
<td>Unpredictable“ Off” Periods</td>
<td>Increase agonist or levodopa</td>
</tr>
<tr>
<td></td>
<td>Liquid sinemet or lisuride infusions</td>
</tr>
<tr>
<td></td>
<td>Apomorphine injections</td>
</tr>
<tr>
<td>Delayed Onset of Drug</td>
<td>Administer 2 hours prior to meals</td>
</tr>
<tr>
<td></td>
<td>Avoid high protein meals</td>
</tr>
<tr>
<td></td>
<td>Crush sinemet and put in a carbonated or acidic drink</td>
</tr>
<tr>
<td></td>
<td>Search and treat GI motility disorder</td>
</tr>
</tbody>
</table>

Table 2
## Dyskinesias and Dystonia in PD

<table>
<thead>
<tr>
<th>Type of Dyskinesia</th>
<th>Possible Treatment Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Dose Dyskinesia</td>
<td>Reduce levodopa, change dosing intervals</td>
</tr>
<tr>
<td></td>
<td>Add dopamine agonist and reduce levodopa</td>
</tr>
<tr>
<td></td>
<td>Addition of amantadine</td>
</tr>
<tr>
<td>Diphasic Dyskinesia (both before and after peak dose)</td>
<td>Change dosing intervals (change peaks/nadirs)</td>
</tr>
<tr>
<td></td>
<td>Adjust levodopa dose</td>
</tr>
<tr>
<td></td>
<td>Add an agonist</td>
</tr>
<tr>
<td></td>
<td>Consider surgery</td>
</tr>
<tr>
<td>Early AM Dystonia (Off Dystonia)</td>
<td>Dose of CR at bedtime</td>
</tr>
<tr>
<td></td>
<td>Dose of levodopa in early AM prior to arising</td>
</tr>
<tr>
<td></td>
<td>Dopamine agonist</td>
</tr>
<tr>
<td></td>
<td>Occasionally baclofen or anticholinergic</td>
</tr>
<tr>
<td>Yo-Yo-ing (Continuous fluctuations)</td>
<td>Dopamine agonists</td>
</tr>
<tr>
<td></td>
<td>Liquid sinemet with frequent doses</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Treat only if bothersome</td>
</tr>
<tr>
<td></td>
<td>Benzodiazepine (Clonazepam)</td>
</tr>
<tr>
<td></td>
<td>Adjust levodopa or agonist dose</td>
</tr>
<tr>
<td></td>
<td>Check to see if on an SSRI</td>
</tr>
<tr>
<td>“Off” Dystonia”</td>
<td>Increase levodopa</td>
</tr>
<tr>
<td></td>
<td>Increase agonist</td>
</tr>
<tr>
<td></td>
<td>Consider anticholinergic or relaxant</td>
</tr>
<tr>
<td></td>
<td>Consider botulinum toxin</td>
</tr>
<tr>
<td>Orofacial Dyskinesia</td>
<td>Decrease levodopa or agonist</td>
</tr>
<tr>
<td></td>
<td>Atypical antipsychotic</td>
</tr>
<tr>
<td></td>
<td>Anticholinergic</td>
</tr>
</tbody>
</table>

**Table 3**
Factors that Should be Considered Prior to PD Surgery that may Contribute to Poor Outcome

Age  
Comorbidities  
Cognitive decline  
Hallucinations  
Poor Response to levodopa  
Not idiopathic PD (e.g. Parkinson’s plus syndrome)  
A particular symptom important to the patient is levodopa unresponsive; (with the notable exception of tremor)  
Emotionally unstable patient  
Patient with unrealistic expectations of surgery  
Severe cerebral atrophy or increased ventricular size

Table 4
References


52. Crossman, A.R., *A hypothesis on the pathophysiological mechanisms that underlie levodopa- or dopamine agonist-induced dyskinesia in Parkinson's*


