



Parkinson's Disease

Parkinson's disease (also known as Parkinson disease or PD) is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills and speech, as well as other functions.

Parkinson's disease belongs to a group of conditions called movement disorders. It is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia) and, in extreme cases, a loss of physical movement (akinesia). The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. Secondary symptoms may include high level cognitive dysfunction and subtle language problems. PD is both chronic and progressive.

PD is the most common cause of chronic progressive parkinsonism, a term which refers to the syndrome of tremor, rigidity, bradykinesia and postural instability. PD is also called "primary parkinsonism" or "idiopathic PD" (classically meaning having no known cause although this term is not strictly true in light of the plethora of newly discovered genetic mutations). While many forms of parkinsonism are "idiopathic", "secondary" cases may result from toxicity most notably of drugs, head trauma, or other medical disorders. The disease is named after English physician James Parkinson; who made a detailed description of the disease in his essay: "An Essay on the Shaking Palsy" (1817).

Signs and Symptoms

Parkinson disease affects movement (motor symptoms). Typical other symptoms include disorders of mood, behavior, thinking, and sensation (non-motor symptoms). Patients' individual symptoms may be quite dissimilar and progression of the disease is also distinctly individual.

Motor symptoms

- *Tremor*: normally 4-6 Hz tremor, maximal when the limb is at rest, and decreased with voluntary movement. It is typically unilateral at onset. This is the most apparent and well-known symptom, though an estimated 30% of patients have little perceptible tremor; these are classified as akinetic-rigid.
- *Rigidity*: stiffness; increased muscle tone. In combination with a resting tremor, this produces a ratchety, "cogwheel" rigidity when the limb is passively moved.
- *bradykinesia/Akinesia*: respectively, slowness or absence of movement. Rapid, repetitive movements produce a dysrhythmic and decremental loss of amplitude.
- *Postural instability*: failure of postural reflexes, which leads to impaired balance and falls.

Other motor symptoms include:

- Gait and posture disturbances:
- Shuffling: gait is characterized by short steps, with feet barely leaving the ground, producing an audible shuffling noise. Small obstacles tend to cause the patient to trip.
- Decreased arm-swing.
- Turning "en bloc": rather than the usual twisting of the neck and trunk and pivoting on the toes, PD patients keep their neck and trunk rigid, requiring multiple small steps to accomplish a turn.
- Stooped, forward-flexed posture. In severe forms, the head and upper shoulders may be bent at a right angle relative to the trunk (camptocormia).
- Festination: a combination of stooped posture, imbalance, and short steps. It leads to a gait that gets progressively faster and faster, often ending in a fall.
- Gait freezing: "freezing" is a manifestation of akinesia (an inability to move). Gait freezing is characterized by an inability to move the feet which may worsen in tight, cluttered spaces or when attempting to initiate gait.
- Dystonia (in about 20% of cases): abnormal, sustained, painful twisting muscle contractions, often affecting the foot and ankle (mainly toe flexion and foot inversion) which often interferes with gait.

- Speech and swallowing disturbances.
- Hypophonia: soft speech. Speech quality tends to be soft, hoarse, and monotonous. Some people with Parkinson's disease claim that their tongue is "heavy" or have cluttered speech.
- Monotonic speech.
- Festinating speech: excessively rapid, soft, poorly-intelligible speech.
- Drooling: most likely caused by a weak, infrequent swallow and stooped posture.
- Non-motor causes of speech/language disturbance in both expressive and receptive language: these include decreased verbal fluency and cognitive disturbance especially related to comprehension of emotional content of speech and of facial expression.
- Dysphagia: impaired ability to swallow. Can lead to aspiration, pneumonia.
- Other motor symptoms:
- Fatigue (up to 50% of cases);
- Masked faces (a mask-like face also known as hypomimia), with infrequent blinking;

- Difficulty rolling in bed or rising from a seated position;
- Micrographia (small, cramped handwriting);
- Impaired fine motor dexterity and motor coordination;
- Impaired gross motor coordination;
- Poverty of movement: overall loss of accessory movements, such as decreased arm swing when walking, as well as spontaneous movement;
- Akathisia.

Non-motor symptoms

Mood disturbances

Estimated prevalence rates of depression vary widely according to the population sampled and methodology used. Reviews of depression estimate its occurrence in anywhere from 20-80% of cases. Estimates from community samples tend to find lower rates than from specialist centres. Most studies use self-report questionnaires such as the Beck Depression Inventory, which may overinflate scores due to physical symptoms. Studies using diagnostic interviews by trained psychiatrists

also report lower rates of depression. More generally, there is an increased risk for any individual with depression to go on to develop Parkinson's disease at a later date. Seventy percent of individuals with Parkinson's disease diagnosed with pre-existing depression go on to develop anxiety. Ninety percent of Parkinson's disease patients with pre-existing anxiety subsequently develop depression; apathy or abulia.

Cognitive disturbances

- Slowed reaction time; both voluntary and involuntary motor responses are significantly slowed.
- Executive dysfunction, characterized by difficulties in: differential allocation of attention, impulse control, set shifting, prioritizing, evaluating the salience of ambient data, interpreting social cues, and subjective time awareness. This complex is present to some degree in most Parkinson's patients; it may progress to:
- Dementia: a later development in approximately 20-40% of all patients, typically starting with slowing of thought and progressing to difficulties with abstract thought, memory, and behavioral regulation. Hallucinations, delusions and paranoia may develop.
- Short term memory loss; procedural memory is more impaired than declarative memory. Prompting elicits improved recall.

- Medication effects: some of the above cognitive disturbances are improved by dopaminergic medications, while others are actually worsened.

Sleep disturbances

- Excessive daytime somnolence
- Initial, intermediate, and terminal insomnia
- Disturbances in REM sleep: disturbingly vivid dreams, and REM Sleep Disorder, characterized by acting out of dream content – can occur years prior to diagnosis

Sensation disturbances

Impaired visual contrast sensitivity, spatial reasoning, colour discrimination, convergence insufficiency (characterized by double vision) and oculomotor control

- Dizziness and fainting; usually attributable orthostatic hypotension, a failure of the autonomic nervous system to adjust blood pressure in response to changes in body position
- Impaired proprioception (the awareness of bodily position in three-dimensional space)
- Reduction or loss of sense of smell (microsmia or anosmia) - can occur years prior to diagnosis
- pain: neuropathic, muscle, joints, and tendons, attributable to tension, dystonia, rigidity, joint stiffness, and injuries associated with attempts at accommodation

Autonomic disturbances

- Oily skin and seborrheic dermatitis.
- Urinary incontinence, typically in later disease progression
- Nocturia (getting up in the night to pass urine) – up to 60% of cases
- Constipation and gastric dysmotility that is severe enough to endanger comfort and even health

- Altered sexual function: characterized by profound impairment of sexual arousal, behavior, orgasm, and drive is found in mid and late Parkinson disease. Current data addresses male sexual function almost exclusively.
- Weight loss, which is significant over a period of ten years.

Diagnosis

There are currently no blood or laboratory tests that have been proven to help in diagnosing PD. Therefore the diagnosis is based on medical history and a neurological examination. The disease can be difficult to diagnose accurately. The Unified Parkinson's Disease Rating Scale is the primary clinical tool used to assist in diagnosis and determine severity of PD. Indeed, only 75% of clinical diagnoses of PD are confirmed at autopsy. Early signs and symptoms of PD may sometimes be dismissed as the effects of normal aging. The physician may need to observe the person for some time until it is apparent that the symptoms are consistently present. Usually doctors look for shuffling of feet and lack of swing in the arms. Doctors may sometimes request brain scans or laboratory tests in order to rule out other diseases. However, CT and MRI brain scans of people with PD usually appear normal.

Clinical practice guidelines introduced in the UK in 2006 state that the diagnosis and follow-up of Parkinson's disease should be done by a specialist in the disease, usually a neurologist with an interest in movement disorders.

Classification

"Parkinson's disease" is the synonym of "primary parkinsonism", i.e. isolated parkinsonism due to a neurodegenerative process without any secondary systemic cause. In some cases, it would be inaccurate to say that the cause is "unknown", because a small proportion is caused by genetic mutations. It is possible for a patient to be initially diagnosed with Parkinson's disease but then to develop additional features, requiring revision of the diagnosis.

There are other disorders that are called *Parkinson-plus diseases*. These include: multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). Some include dementia with Lewy bodies (DLB) – while idiopathic Parkinson's disease patients also have Lewy bodies in their brain tissue, the distribution is denser and more widespread in DLB. Even so, the relationship between Parkinson disease, Parkinson disease with dementia (PDD), and dementia with Lewy bodies (DLB) might be most accurately conceptualized as a spectrum, with a discrete area of overlap between each of the three disorders. The natural history and role of Lewy bodies is little understood.

These Parkinson-plus diseases may progress more quickly than typical idiopathic Parkinson disease. If cognitive dysfunction occurs before or very early in the course of the movement disorder then DLBD may be suspected. Early postural instability with minimal tremor especially in the context of ophthalmoparesis should suggest PSP. Early autonomic dysfunction including erectile dysfunction and syncope may suggest MSA. The presence of extreme asymmetry with patchy cortical cognitive defects such dysphasia and apraxias especially with "alien limb" phenomena should suggest CBD.

The usual anti-Parkinson's medications are typically either less effective or not effective at all in controlling symptoms; patients may be exquisitely sensitive to neuroleptic medications like haloperidol. Additionally, the cholinesterase inhibiting medications have shown preliminary efficacy in treating the cognitive, psychiatric, and behavioral aspects of the disease, so correct differential diagnosis is important.

Essential tremor may be mistaken for Parkinson's disease but lacks all other features besides tremor, and has particular characteristics distinguishing it from Parkinson's, such as improvement with beta blockers and alcoholic beverages.

Wilson's disease (hereditary copper accumulation) may present with parkinsonistic features; young patients presenting with parkinsonism or any other movement disorder are frequently screened for this rare condition, because it may respond to medical treatment. Typical tests are liver function, slit lamp examination for Kayser-Fleisher rings, and serum ceruloplasmin levels.

Pathology

Dopaminergic pathways of the human brain in normal condition (left) and Parkinson's disease (right). Red Arrows indicate suppression of the target, blue arrows indicate stimulation of target structure.

The symptoms of Parkinson's disease result from the loss of pigmented dopamine-secreting (dopaminergic) cells in the pars compacta region of the substantia nigra (literally "black substance"). These neurons project to the striatum and their loss leads to alterations in the activity of the neural circuits within the basal ganglia that regulate movement, in essence an inhibition of the direct pathway and excitation of the indirect pathway.

The direct pathway facilitates movement and the indirect pathway inhibits movement, thus the loss of these cells leads to a hypokinetic movement disorder. The lack of dopamine results in increased inhibition of the ventral anterior nucleus of the thalamus, which sends excitatory projections to the motor cortex, thus leading to hypokinesia.

There are four major dopamine pathways in the brain; the nigrostriatal pathway, referred to above, mediates movement and is the most conspicuously affected in early Parkinson's disease. The other pathways are the mesocortical, the mesolimbic, and the tuberoinfundibular. Disruption of dopamine along the non-striatal pathways likely explains much of the neuropsychiatric pathology associated with Parkinson's disease.

The mechanism by which the brain cells in Parkinson's are lost may consist of an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells. The alpha-synuclein-ubiquitin complex cannot be directed to the proteasome. This protein accumulation forms proteinaceous cytoplasmic inclusions called Lewy bodies. Latest research on pathogenesis of disease has shown that the death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins between two major cellular organelles – the endoplasmic reticulum (ER) and the Golgi apparatus. Certain proteins like Rab1 may reverse this defect caused by alpha-synuclein in animal models.

Excessive accumulations of iron, which are toxic to nerve cells, are also typically observed in conjunction with the protein inclusions. Iron and other transition metals such as copper bind to neuromelanin in the affected neurons of the substantia nigra. Neuromelanin may be acting as a protective agent. The most likely mechanism is generation of reactive oxygen species. Iron also induces aggregation of synuclein by oxidative mechanisms. Similarly, dopamine and the byproducts of dopamine production enhance alpha-synuclein aggregation. The precise mechanism whereby such aggregates of alpha-synuclein damage the cells is not known. The aggregates may be merely a normal reaction by the cells as part of their effort to correct a different, as-yet unknown, insult. Based on this mechanistic hypothesis, a transgenic mouse model of Parkinson's has been generated by introduction of human wild-type alpha-synuclein into the mouse genome under control of the platelet-derived-growth factor- β promoter.

Causes

Most people with Parkinson's disease are described as having idiopathic Parkinson's disease (having no specific cause). There are far less common causes of Parkinson's disease including genetic, toxins, head trauma, cerebral anoxia, and drug-induced Parkinson's disease.

Genetic

In recent years, a number of specific genetic mutations causing Parkinson's disease have been discovered, including in certain populations (Contursi, Italy). These account for a small minority of cases of Parkinson's disease. Someone who has Parkinson's disease is more likely to have relatives that also have Parkinson's disease. However, this does not mean that the disorder has been passed on genetically.

Genetic forms that have been identified include (*external links in this section are to Online Mendelian Inheritance in Man*):

Type

OMIM

Locus

Details

PARK1

OMIM #168601

4q21

caused by mutations in the *SNCA* gene, which codes for the protein alpha-synuclein. *PARK1* causes autosomal dominant Parkinson disease. So-called *PARK4* (OMIM #605543) is probably caused by triplication of *SNCA*.

PARK2

OMIM *602544

6q25.2-q27

caused by mutations in protein parkin. Parkin mutations may be one of the most common known genetic causes of early-onset Parkinson disease. In one study, of patients with onset of Parkinson disease prior to age 40 (10% of all PD patients), 18% had parkin mutations, with 5% homozygous mutations. Patients with an autosomal recessive family history of parkinsonism are much more likely to carry parkin mutations if age at onset is less than 20 (80% vs. 28% with onset over age 40). Patients with parkin mutations (*PARK2*) do not have Lewy bodies. Such patients develop a syndrome that closely resembles the sporadic form of PD; however, they tend to develop symptoms at a much younger age.

PARK3

OMIM %602404

2p13

autosomal dominant, only described in a few kindreds.

PARK5

OMIM +191342

4p14

caused by mutations in the *UCHL1* gene which codes for the protein ubiquitin carboxy-terminal hydrolase L1

PARK6

OMIM #605909

1p36

caused by mutations in *PINK1* (OMIM *608309) which codes for the protein PTEN-induced putative kinase 1.

PARK7

OMIM #606324

1p36

caused by mutations in DJ-1 (OMIM 602533)

PARK8

OMIM #607060

12q12

caused by mutations in LRRK2 which codes for the protein dardarin. *In vitro*, mutant LRRK2 causes protein aggregation and cell death, possibly through an interaction with parkin. LRRK2 mutations, of which the most common is G2019S, cause autosomal dominant Parkinson disease, with a penetrance of nearly 100% by age 80. G2019S is the most common known genetic cause of Parkinson disease, found in 1-6% of U.S. and European PD patients. It is especially common in Ashkenazi Jewish patients, with a prevalence of 29.7% in familial cases and 13.3% in sporadic.

PARK9

OMIM #606693

1p36

Caused by mutations in the *ATP13A2* gene, and also known as Kufor-Rakeb Syndrome. PARK9 may be allelic to PARK6.

PARK10

OMIM %606852

1p

-

PARK11

OMIM %607688

2q36-37

However, this gene locus has conflicting data, and may not have significance.

PARK12

OMIM %300557

Xq21-q25

-

PARK13

OMIM #610297

2p12

Caused by mutations in the *HTRA2* (HtrA serine peptidase 2) gene.

Toxins

One theory holds that the disease may result in many or even most cases from the combination of a genetically determined vulnerability to environmental toxins along with exposure to those toxins. This hypothesis is consistent with the fact that Parkinson's disease is not distributed homogeneously throughout the population; its incidence varies geographically. However, it is not consistent with the fact that the first appearance of the syndrome predates the first synthesis of the compounds often attributed to causing Parkinson's disease. The toxins most strongly suspected at present are certain pesticides and transition-series metals such as manganese or iron, especially those that generate reactive oxygen species, and/or bind to neuromelanin, as originally suggested by G.C. Cotzias. In the Cancer Prevention Study II Nutrition Cohort, a longitudinal investigation, individuals who were exposed to pesticides had a 70% higher incidence of PD than individuals who were not exposed.

MPTP (pro-toxin N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is used as a model for Parkinson's, as it can rapidly induce parkinsonian symptoms in human beings and other animals of any age. MPTP was notorious for a string of Parkinson's disease cases in California in 1982 when it contaminated the illicit production of the synthetic opiate MPPP. Its toxicity likely comes from generation of reactive oxygen species through tyrosine hydroxylation.

Other toxin-based models employ PCBs, paraquat (a herbicide) in combination with maneb (a fungicide), rotenone (an insecticide), and specific organochlorine pesticides including dieldrin and lindane. Rotenone is an inhibitor of complex 1 of the electron transport chain. It easily crosses membranes due to its extremely hydrophobic properties. Rotenone, therefore, does not rely on the dopamine transporter to enter into the cytoplasm. Numerous studies have found an increase in PD in persons who consume rural well water; researchers theorize that water consumption is a proxy measure of pesticide exposure. In agreement with this hypothesis are studies which have found a dose-dependent increase in PD in persons exposed to agricultural chemicals.

Head trauma

Past episodes of head trauma are reported more frequently by individuals with Parkinson's disease than by others in the population. A recent methodologically strong retrospective study found that those who have experienced a head injury are four times more likely to develop Parkinson's disease than those who have never suffered a head injury. The risk of developing Parkinson's increases eightfold for patients who have had head trauma requiring hospitalization, and it increases 11-fold for patients who have experienced severe head injury. The authors comment that since head trauma is a rare event, the contribution to PD incidence is slight. They express further concern that their results may be biased by recall, i.e., the PD patients because they reflect upon the causes of their illness, may remember head trauma better than the non-ill control subjects. These limitations were overcome recently by Tanner and colleagues, who found a similar risk of 3.8, with increasing risk associated with more severe injury and hospitalization.

Treatment

Parkinson's disease is a chronic disorder that requires broad-based management including patient and family education, support group services, general wellness maintenance, physiotherapy, exercise, and nutrition. At present, there is no cure for PD, but medications or surgery can provide relief from the symptoms.

Levodopa

Stalevo for treatment of Parkinson's disease

The most widely used form of treatment is L-dopa in various forms. L-dopa is transformed into dopamine in the dopaminergic neurons by L-aromatic amino acid decarboxylase (often known by its former name dopa-decarboxylase). However, only 1-5% of L-DOPA enters the dopaminergic neurons. The remaining L-DOPA is often metabolised to dopamine elsewhere, causing a wide variety of side effects. Due to feedback inhibition, L-dopa results in a reduction in the endogenous formation of L-dopa, and so eventually becomes counterproductive.

Carbidopa and benserazide are dopa decarboxylase inhibitors. They help to prevent the metabolism of L-dopa before it reaches the dopaminergic neurons and are generally given as combination preparations of carbidopa/levodopa (co-careldopa) (e.g. Sinemet, Parcopa) and benserazide/levodopa (co-beneldopa) (e.g. Madopar). There are also controlled release versions of Sinemet and Madopar that spread out the effect of the L-dopa. Duodopa is a combination of levodopa and carbidopa, dispersed as a viscous gel. Using a patient-operated portable pump, the drug is continuously delivered via a tube directly into the upper small intestine, where it is rapidly absorbed. There is also Stalevo (Carbidopa, Levodopa and Entacapone).

Tolcapone inhibits the COMT enzyme, thereby prolonging the effects of L-dopa, and so has been used to complement L-dopa. However, due to its possible side effects such as liver failure, it's limited in its availability.

A similar drug, entacapone, has similar efficacy and has not been shown to cause significant alterations of liver function. A recent follow-up study by Cilia and colleagues looked at the clinical effects of long-term administration of entacapone, on motor performance and pharmacological compensation, in advanced PD patients with motor fluctuations: 47 patients with advanced PD and motor fluctuations were followed for six years from the first prescription of entacapone and showed a stabilization of motor conditions, reflecting entacapone can maintain adequate inhibition of COMT over time.

Mucuna pruriens, is a natural source of therapeutic quantities of L-dopa, and has been under some investigation.

Dopamine agonists

The dopamine agonists bromocriptine, pergolide, pramipexole, ropinirole, cabergoline, apomorphine, and lisuride are moderately effective. These have their own side effects including those listed above in addition to somnolence, hallucinations and/or insomnia. Several forms of dopamine agonism have been linked with a markedly increased risk of problem gambling. Dopamine agonists initially act by stimulating some of the dopamine receptors. However, they cause the dopamine receptors to become progressively less sensitive, thereby eventually increasing the symptoms.

Dopamine agonists can be useful for patients experiencing on-off fluctuations and dyskinesias as a result of high doses of L-dopa. Apomorphine can be administered via subcutaneous injection using a small pump which is carried by the patient. A low dose is automatically administered throughout the day, reducing the fluctuations of motor symptoms by providing a steady dose of dopaminergic stimulation. After an initial "apomorphine challenge" in hospital to test its effectiveness and brief patient and primary caregiver (often a spouse or partner), the latter of whom takes over maintenance of the pump. The injection site must be changed daily and rotated around the body to avoid the formation of nodules. Apomorphine is also available in a more acute dose as an autoinjector pen for emergency doses such as after a fall or first thing in the morning. Nausea and vomiting are common, any may require domperidone (an antiemetic).

MAO-B inhibitors

Selegiline and rasagiline reduce the symptoms by inhibiting monoamine oxidase-B (MAO-B), which inhibits the breakdown of dopamine secreted by the dopaminergic neurons. Metabolites of selegiline include L-amphetamine and L-methamphetamine (not to be confused with the more notorious and potent dextrorotary isomers). This might result in side effects such as insomnia.

Use of L-dopa in conjunction with selegiline has increased mortality rates that have not been effectively explained. Another side effect of the combination can be stomatitis. One report raised concern about increased mortality when MAO-B inhibitors were combined with L-dopa; however subsequent studies have not confirmed this finding. Unlike other non selective monoamine oxidase inhibitors, tyramine-containing foods do not cause a hypertensive crisis.

Speech therapies

The most widely practiced treatment for the speech disorders associated with Parkinson's disease is Lee Silverman Voice Treatment (LSVT). LSVT focuses on increasing vocal loudness.

A study found that an electronic device providing frequency-shifted auditory feedback (FAF) improved the clarity of Parkinson's patients' speech.

Physical exercise

Regular physical exercise and/or therapy, including yoga, tai chi, and dance, can be beneficial to the patient for maintaining and improving mobility, flexibility, balance, and range of motion. Physicians and physical therapists often recommend basic exercises, such as bringing the toes up with every step, carrying a bag with weight to decrease the bend on one side, and practicing chewing hard and moving the food around the mouth.

Surgery and deep brain stimulation

Treating Parkinson's disease with surgery was once a common practice, but after the discovery of levodopa, surgery was restricted to only a few cases. Studies in the past few decades have led to great improvements in surgical techniques, and surgery is again being used in people with advanced PD for whom drug therapy is no longer sufficient.

Deep brain stimulation is presently the most used surgical means of treatment, but other surgical therapies that have shown promise include surgical lesion of the subthalamic nucleus and of the internal segment of the globus pallidus, a procedure known as pallidotomy.

Methods undergoing evaluation

Gene therapy

Currently under investigation is gene therapy. This involves using a non-infectious virus to shuttle a gene into a part of the brain called the subthalamic nucleus (STN). The gene used leads to the production of an enzyme called glutamic acid decarboxylase (GAD), which catalyses the production of a neurotransmitter called GABA. GABA acts as a direct inhibitor on the overactive cells in the STN.

GDNF infusion involves the infusion of GDNF (glial-derived neurotrophic factor) into the basal ganglia using surgically implanted catheters. Via a series of biochemical reactions, GDNF stimulates the formation of L-dopa. GDNF therapy is still in development.

Implantation of stem cells genetically engineered to produce dopamine or stem cells that transform into dopamine-producing cells has already started being used. These could not constitute cures because they do not address the considerable loss of activity of the dopaminergic neurons. Initial results have been unsatisfactory, with patients still retaining their drugs and symptoms.

Neuroprotective treatments

Neuroprotective treatments are at the forefront of PD research, but are still under clinical scrutiny. These agents could protect neurons from cell death induced by disease presence resulting in a slower progression of disease. Agents currently under investigation as neuroprotective agents include apoptotic drugs (CEP 1347 and CTCT346), lazaroids, bioenergetics, antiglutamatergic agents and dopamine receptors. Clinically evaluated neuroprotective agents are the monoamine oxidase inhibitors selegiline and rasagiline, dopamine agonists, and the complex I mitochondrial fortifier coenzyme Q10.

Neural transplantation

The first prospective randomised double-blind sham-placebo controlled trial of dopamine-producing cell transplants failed to show an improvement in quality of life although some significant clinical improvements were seen in patients below the age of 60. A significant problem was the excess release of dopamine by the transplanted tissue, leading to dystonias. Research in African green monkeys suggests that the use of stem cells might in future provide a similar benefit without inducing dystonias.

Nutrients

Nutrients have been used in clinical studies and are widely used by people with Parkinson's disease in order to partially treat PD or slow down its deterioration. The L-dopa precursor L-tyrosine was shown to relieve an average of 70% of symptoms. Ferrous iron, the essential cofactor for L-dopa biosynthesis was shown to relieve between 10% and 60% of symptoms in 110 out of 110 patients.

More limited efficacy has been obtained with the use of THFA, NADH, and pyridoxine—coenzymes and coenzyme precursors involved in dopamine biosynthesis. Vitamin C and vitamin E in large doses are commonly used by patients in order to theoretically lessen the cell damage that occurs in Parkinson's disease. This is because the enzymes superoxide dismutase and catalase require these vitamins in order to nullify the superoxide anion, a toxin commonly produced in damaged cells. However, in the randomized controlled trial, DATATOP of patients with early PD, no beneficial effect for vitamin E compared to placebo was seen.

Coenzyme Q10 has more recently been used for similar reasons. MitoQ

is a newly developed synthetic substance that is similar in structure and function to coenzyme Q10.

Qigong

There have been two studies looking at qigong in Parkinson's disease. In a trial in Bonn, an open-label randomised pilot study in 56 patients found an improvement in motor and non-motor symptoms amongst patients who had undergone one hour of structured qigong exercise per week in two 8-week blocks. The authors speculate that visualizing the flow of "energy" might act as an internal cue and so help improve movement.

The second study, however, found qigong to be ineffective in treating Parkinson's disease. In that study, researchers used a randomized cross-over trial to compare aerobic training with qigong in advanced Parkinson's disease. Two groups of PD patients were assessed, had 20 sessions of either aerobic exercise or qigong, were assessed again, then after a 2-month gap were switched over for another 20 sessions, and finally assessed again. The authors found an improvement in motor ability and cardiorespiratory function following aerobic exercise, but found no benefit following qigong. The authors also point out that aerobic exercise had no benefit for patients' quality of life.

Botox

Recently, Botox injections are being investigated as a non-FDA approved possible experimental treatment.

Prognosis

PD is not considered to be a fatal disease by itself, but it progresses with time. The average life expectancy of a PD patient is generally lower than for people who do not have the disease. In the late stages of the disease, PD may cause complications such as choking, pneumonia, and falls that can lead to death.

The progression of symptoms in PD may take 20 years or more. In some people, however, the disease progresses more quickly. There is no way to predict what course the disease will take for an individual person. With appropriate treatment, most people with PD can live productive lives for many years after diagnosis.

In at least some studies, it has been observed that mortality was significantly increased, and longevity decreased among nursing home patients as compared to community dwelling patients.

One commonly used system for describing how the symptoms of PD progress is called the Hoehn and Yahr scale. Another commonly used scale is the Unified Parkinson's Disease Rating Scale (UPDRS). This much more complicated scale has multiple ratings that measure motor function, and also mental functioning, behavior, mood, and activities of daily living; and motor function. Both the Hoehn and Yahr scale and the UPDRS are used to measure how individuals are faring and how much treatments are helping them. It should be noted that neither scale is specific to Parkinson's disease; that patients with other illnesses can score in the Parkinson's range.