

= Parkinson 's disease =

Parkinson 's disease (PD) is a long term disorder of the central nervous system that mainly affects the motor system . The symptoms generally come on slowly over time . Early in the disease , the most obvious are shaking , rigidity , slowness of movement , and difficulty with walking . Thinking and behavioral problems may also occur . Dementia becomes common in the advanced stages of the disease . Depression and anxiety are also common occurring in more than a third of people with PD . Other symptoms include sensory , sleep , and emotional problems . The main motor symptoms are collectively called " parkinsonism " , or a " parkinsonian syndrome " .

The cause of Parkinson 's disease is generally unknown , but believed to involve both genetic and environmental factors . Those with a family member affected are more likely to get the disease themselves . There is also an increased risk in people exposed to certain pesticides and among those who have had prior head injuries while there is a reduced risk in tobacco smokers and those who drink coffee or tea . The motor symptoms of the disease result from the death of cells in the substantia nigra , a region of the midbrain . This results in not enough dopamine in these areas . The reason for this cell death is poorly understood but involves the build up of proteins into Lewy bodies in the neurons . Diagnosis of typical cases is mainly based on symptoms , with tests such as neuroimaging being used to rule out other diseases .

There is no cure for Parkinson 's disease . Initial treatments is typically with the antiparkinson medication levodopa , with dopamine agonists being used once levodopa becomes less effective . As the disease progresses and neurons continue to be lost , these medications become less effective while at the same time they produce a complication marked by involuntary writhing movements . Diet and some forms of rehabilitation have shown some effectiveness at improving symptoms . Surgery to place the microelectrodes for deep brain stimulation has been used to reduce motor symptoms in severe cases where drugs are ineffective . Evidence for treatments for the non movement related symptoms of PD , such as sleep disturbances and emotional problems , is less strong .

In 2013 PD was present in 53 million people and resulted in about 103 000 deaths globally . Parkinson 's disease typically occurs in people over the age of 60 , of which about one percent are affected . Males are more often affected than females . When it is seen in people before the age of 40 or 50 , it is called young onset PD . The average life expectancy following diagnosis is between 7 and 14 years . The disease is named after the English doctor James Parkinson , who published the first detailed description in An Essay on the Shaking Palsy , in 1817 . Public awareness campaigns include World Parkinson 's Day (on the birthday of James Parkinson , 11 April) and the use of a red tulip as the symbol of the disease . People with parkinsonism who have increased the public 's awareness of the condition include actor Michael J. Fox , Olympic cyclist Davis Phinney , and late professional boxer Muhammad Ali .

= = Classification = =

The term parkinsonism is used for a motor syndrome whose main symptoms are tremor at rest , stiffness , slowing of movement and postural instability . Parkinsonian syndromes can be divided into four subtypes , according to their origin :

primary or idiopathic

secondary or acquired

hereditary parkinsonism , and

Parkinson plus syndromes or multiple system degeneration .

Parkinson 's disease is the most common form of parkinsonism and is usually defined as " primary " parkinsonism , meaning parkinsonism with no external identifiable cause . In recent years several genes that are directly related to some cases of Parkinson 's disease have been discovered . As much as this conflicts with the definition of Parkinson 's disease as an idiopathic illness , genetic parkinsonism disorders with a similar clinical course to PD are generally included under the Parkinson 's disease label . The terms " familial Parkinson 's disease " and " sporadic Parkinson 's

disease " can be used to differentiate genetic from truly idiopathic forms of the disease .

Usually classified as a movement disorder , PD also gives rise to several non motor types of symptoms such as sensory deficits , cognitive difficulties , and sleep problems . Parkinson plus diseases are primary parkinsonisms which present additional features . They include multiple system atrophy , progressive supranuclear palsy , corticobasal degeneration , and dementia with Lewy bodies .

In terms of pathophysiology , PD is considered a synucleinopathy due to an abnormal accumulation of alpha synuclein protein in the brain in the form of Lewy bodies , as opposed to other diseases such as Alzheimer 's disease where the brain accumulates tau protein in the form of neurofibrillary tangles . Nevertheless , there is clinical and pathological overlap between tauopathies and synucleinopathies . The most typical symptom of Alzheimer 's disease , dementia , occurs in advanced stages of PD , while it is common to find neurofibrillary tangles in brains affected by PD .

Dementia with Lewy bodies (DLB) is another synucleinopathy that has similarities with PD , and especially with the subset of PD cases with dementia . However , the relationship between PD and DLB is complex and still has to be clarified . They may represent parts of a continuum or they may be separate diseases .

= = Signs and symptoms = =

Parkinson 's disease affects movement , producing motor symptoms . Non motor symptoms , which include autonomic dysfunction , neuropsychiatric problems (mood , cognition , behavior or thought alterations) , and sensory and sleep difficulties , are also common . Some of these non motor symptoms are often present at the time of diagnosis and can precede motor symptoms .

= = = Motor = = =

Four motor symptoms are considered cardinal in PD : tremor , rigidity , slowness of movement , and postural instability .

Tremor is the most apparent and well known symptom . It is the most common ; though around 30 % of individuals with PD do not have tremor at disease onset , most develop it as the disease progresses . It is usually a rest tremor : maximal when the limb is at rest and disappearing with voluntary movement and sleep . It affects to a greater extent the most distal part of the limb and at onset typically appears in only a single arm or leg , becoming bilateral later . Frequency of PD tremor is between 4 and 6 hertz (cycles per second) . A feature of tremor is pill rolling , the tendency of the index finger of the hand to get into contact with the thumb and perform together a circular movement . The term derives from the similarity between the movement of people with PD and the earlier pharmaceutical technique of manually making pills .

Hypokinesia (slowness of movement) is another characteristic feature of PD , and is associated with difficulties along the whole course of the movement process , from planning to initiation and finally execution of a movement . Performance of sequential and simultaneous movement is hindered . Bradykinesia is commonly a very disabling symptom in the early stages of the disease . Initial manifestations are problems when performing daily tasks which require fine motor control such as writing , sewing or getting dressed . Clinical evaluation is based on similar tasks such as alternating movements between both hands or both feet . Bradykinesia is not equal for all movements or times . It is modified by the activity or emotional state of the subject , to the point that some people are barely able to walk yet can still ride a bicycle . Generally people with PD have less difficulty when some sort of external cue is provided .

Rigidity is stiffness and resistance to limb movement caused by increased muscle tone , an excessive and continuous contraction of muscles . In parkinsonism the rigidity can be uniform (lead pipe rigidity) or ratchety (cogwheel rigidity) . The combination of tremor and increased tone is considered to be at the origin of cogwheel rigidity . Rigidity may be associated with joint pain ; such pain being a frequent initial manifestation of the disease . In early stages of Parkinson 's

disease , rigidity is often asymmetrical and it tends to affect the neck and shoulder muscles prior to the muscles of the face and extremities . With the progression of the disease , rigidity typically affects the whole body and reduces the ability to move .

Postural instability is typical in the late stages of the disease , leading to impaired balance and frequent falls , and secondarily to bone fractures . Instability is often absent in the initial stages , especially in younger people . Up to 40 % may experience falls and around 10 % may have falls weekly , with the number of falls being related to the severity of PD .

Other recognized motor signs and symptoms include gait and posture disturbances such as festination (rapid shuffling steps and a forward @-@ flexed posture when walking) , speech and swallowing disturbances including voice disorders , mask @-@ like face expression or small handwriting , although the range of possible motor problems that can appear is large .

= = = Neuropsychiatric = = =

Parkinson 's disease can cause neuropsychiatric disturbances which can range from mild to severe . This includes disorders of speech , cognition , mood , behaviour , and thought .

Cognitive disturbances can occur in the early stages of the disease and sometimes prior to diagnosis , and increase in prevalence with duration of the disease . The most common cognitive deficit in affected individuals is executive dysfunction , which can include problems with planning , cognitive flexibility , abstract thinking , rule acquisition , initiating appropriate actions and inhibiting inappropriate actions , working memory , and selecting relevant sensory information . Fluctuations in attention , impaired perception and estimation of time , slowed cognitive processing speed are among other cognitive difficulties . Memory is affected , specifically in recalling learned information . Nevertheless , improvement appears when recall is aided by cues . Visuospatial difficulties are also part of the disease , seen for example when the individual is asked to perform tests of facial recognition and perception of the orientation of drawn lines .

A person with PD has two to six times the risk of dementia compared to the general population . The prevalence of dementia increases with duration of the disease . Dementia is associated with a reduced quality of life in people with PD and their caregivers , increased mortality , and a higher probability of needing nursing home care .

Behavior and mood alterations are more common in PD without cognitive impairment than in the general population , and are usually present in PD with dementia . The most frequent mood difficulties are depression , apathy and anxiety . Establishing the diagnosis of depression is complicated by symptoms that often occur in Parkinson 's including dementia , decreased facial expression , decreased movement , a state of indifference , and quiet speech . Impulse control behaviors such as medication overuse and craving , binge eating , hypersexuality , or pathological gambling can appear in PD and have been related to the medications used to manage the disease . Psychotic symptoms ? hallucinations or delusions ? occur in 4 % of people with PD , and it is assumed that the main precipitant of psychotic phenomena in Parkinson 's disease is dopaminergic excess secondary to treatment ; it therefore becomes more common with increasing age and levodopa intake .

= = = Other = = =

In addition to cognitive and motor symptoms , PD can impair other body functions .

Sleep problems are a feature of the disease and can be worsened by medications . Symptoms can manifest as daytime drowsiness , disturbances in REM sleep , or insomnia . A systematic review shows that sleep attacks occur in 13 @.@ 0 % of patients with Parkinson 's disease on dopaminergic medications .

Alterations in the autonomic nervous system can lead to orthostatic hypotension (low blood pressure upon standing) , oily skin and excessive sweating , urinary incontinence and altered sexual function . Constipation and gastric dysmotility can be severe enough to cause discomfort and even endanger health . PD is related to several eye and vision abnormalities such as decreased

blink rate , dry eyes , deficient ocular pursuit (eye tracking) and saccadic movements (fast automatic movements of both eyes in the same direction) , difficulties in directing gaze upward , and blurred or double vision . Changes in perception may include an impaired sense of smell , sensation of pain and paresthesia (skin tingling and numbness) . All of these symptoms can occur years before diagnosis of the disease .

= = Causes = =

Parkinson 's disease in most people is idiopathic (having no specific known cause) . However , a small proportion of cases can be attributed to known genetic factors . Other factors have been associated with the risk of developing PD , but no causal relationships have been proven .

= = = Environmental factors = = =

A number of environmental factors have been associated with an increased risk of Parkinson 's including : pesticide exposure , head injuries , and living in the country or farming . Rural environments and the drinking of well water may be risks as they are indirect measures of exposure to pesticides .

Implicated agents include insecticides , primarily chlorpyrifos and organochlorines and pesticides , such as rotenone or paraquat , and herbicides , such as Agent Orange and ziram . Heavy metals exposure has been proposed to be a risk factor , through possible accumulation in the substantia nigra ; however , studies on the issue have been inconclusive .

= = = Genetics = = =

PD traditionally has been considered a non @-@ genetic disorder ; however , around 15 % of individuals with PD have a first @-@ degree relative who has the disease . At least 5 % of people are now known to have forms of the disease that occur because of a mutation of one of several specific genes .

Mutations in specific genes have been conclusively shown to cause PD . These genes code for alpha @-@ synuclein (SNCA) , parkin (PRKN) , leucine @-@ rich repeat kinase 2 (LRRK2 or dardarin) , PTEN @-@ induced putative kinase 1 (PINK1) , DJ @-@ 1 and ATP13A2 . In most cases , people with these mutations will develop PD . With the exception of LRRK2 , however , they account for only a small minority of cases of PD . The most extensively studied PD @-@ related genes are SNCA and LRRK2 . Mutations in genes including SNCA , LRRK2 and glucocerebrosidase (GBA) have been found to be risk factors for sporadic PD . Mutations in GBA are known to cause Gaucher 's disease . Genome @-@ wide association studies , which search for mutated alleles with low penetrance in sporadic cases , have now yielded many positive results .

The role of the SNCA gene is important in PD because the alpha @-@ synuclein protein is the main component of Lewy bodies . Missense mutations of the gene (in which a single nucleotide is changed) , and duplications and triplications of the locus containing it have been found in different groups with familial PD . Missense mutations are rare . On the other hand , multiplications of the SNCA locus account for around 2 % of familial cases . Multiplications have been found in asymptomatic carriers , which indicate that penetrance is incomplete or age @-@ dependent .

The LRRK2 gene (PARK8) encodes a protein called dardarin . The name dardarin was taken from a Basque word for tremor , because this gene was first identified in families from England and the north of Spain . Mutations in LRRK2 are the most common known cause of familial and sporadic PD , accounting for approximately 5 % of individuals with a family history of the disease and 3 % of sporadic cases . There are many mutations described in LRRK2 , however unequivocal proof of causation only exists for a few .

Several Parkinson @-@ related genes are involved in the function of lysosomes , organelles that digest cellular waste products . It has been suggested that some forms of Parkinson may be caused by lysosome dysfunctions that reduce the ability of cells to break down alpha @-@ synuclein .

= = Pathology = =

= = = Anatomical = = =

The basal ganglia , a group of brain structures innervated by the dopaminergic system , are the most seriously affected brain areas in PD . The main pathological characteristic of PD is cell death in the substantia nigra and , more specifically , the ventral (front) part of the pars compacta , affecting up to 70 % of the cells by the time death occurs .

Macroscopic alterations can be noticed on cut surfaces of the brainstem , where neuronal loss can be inferred from a reduction of neuromelanin pigmentation in the substantia nigra and locus coeruleus . The histopathology (microscopic anatomy) of the substantia nigra and several other brain regions shows neuronal loss and Lewy bodies in many of the remaining nerve cells . Neuronal loss is accompanied by death of astrocytes (star @-@ shaped glial cells) and activation of the microglia (another type of glial cell) . Lewy bodies are a key pathological feature of PD .

= = = Pathophysiology = = =

The primary symptoms of Parkinson 's disease result from greatly reduced activity of dopamine @-@ secreting cells caused by cell death in the pars compacta region of the substantia nigra .

There are five major pathways in the brain connecting other brain areas with the basal ganglia . These are known as the motor , oculo @-@ motor , associative , limbic and orbitofrontal circuits , with names indicating the main projection area of each circuit . All of them are affected in PD , and their disruption explains many of the symptoms of the disease since these circuits are involved in a wide variety of functions including movement , attention and learning . Scientifically , the motor circuit has been examined the most intensively .

A particular conceptual model of the motor circuit and its alteration with PD has been of great influence since 1980 , although some limitations have been pointed out which have led to modifications . In this model , the basal ganglia normally exert a constant inhibitory influence on a wide range of motor systems , preventing them from becoming active at inappropriate times . When a decision is made to perform a particular action , inhibition is reduced for the required motor system , thereby releasing it for activation . Dopamine acts to facilitate this release of inhibition , so high levels of dopamine function tend to promote motor activity , while low levels of dopamine function , such as occur in PD , demand greater exertions of effort for any given movement . Thus , the net effect of dopamine depletion is to produce hypokinesia , an overall reduction in motor output . Drugs that are used to treat PD , conversely , may produce excessive dopamine activity , allowing motor systems to be activated at inappropriate times and thereby producing dyskinesias .

= = = Brain cell death = = =

There is speculation of several mechanisms by which the brain cells could be lost . One mechanism consists of an abnormal accumulation of the protein alpha @-@ synuclein bound to ubiquitin in the damaged cells . This insoluble protein accumulates inside neurones forming inclusions called Lewy bodies . According to the Braak staging , a classification of the disease based on pathological findings , Lewy bodies first appear in the olfactory bulb , medulla oblongata and pontine tegmentum , with individuals at this stage being asymptomatic . As the disease progresses , Lewy bodies later develop in the substantia nigra , areas of the midbrain and basal forebrain , and in a last step the neocortex . These brain sites are the main places of neuronal degeneration in PD ; however , Lewy bodies may not cause cell death and they may be protective . In people with dementia , a generalized presence of Lewy bodies is common in cortical areas . Neurofibrillary tangles and senile plaques , characteristic of Alzheimer 's disease , are not common unless the person is demented .

Other cell @-@ death mechanisms include proteosomal and lysosomal system dysfunction and

reduced mitochondrial activity . Iron accumulation in the substantia nigra is typically observed in conjunction with the protein inclusions . It may be related to oxidative stress , protein aggregation and neuronal death , but the mechanisms are not fully understood .

= = Diagnosis = =

A physician will diagnose Parkinson 's disease from the medical history and a neurological examination . There is no lab test that will clearly identify the disease , but brain scans are sometimes used to rule out disorders that could give rise to similar symptoms . People may be given levodopa and resulting relief of motor impairment tends to confirm the diagnosis . The finding of Lewy bodies in the midbrain on autopsy is usually considered proof that the person had Parkinson 's disease . The progress of the illness over time may reveal it is not Parkinson 's disease , and some authorities recommend that the diagnosis should be periodically reviewed .

Other causes that can secondarily produce a parkinsonian syndrome are Alzheimer 's disease , multiple cerebral infarction and drug @-@ induced parkinsonism . Parkinson plus syndromes such as progressive supranuclear palsy and multiple system atrophy must be ruled out . Anti @-@ Parkinson 's medications are typically less effective at controlling symptoms in Parkinson plus syndromes . Faster progression rates , early cognitive dysfunction or postural instability , minimal tremor or symmetry at onset may indicate a Parkinson plus disease rather than PD itself . Genetic forms are usually classified as PD , although the terms familial Parkinson 's disease and familial parkinsonism are used for disease entities with an autosomal dominant or recessive pattern of inheritance .

Medical organizations have created diagnostic criteria to ease and standardize the diagnostic process , especially in the early stages of the disease . The most widely known criteria come from the UK Parkinson 's Disease Society Brain Bank and the U.S. National Institute of Neurological Disorders and Stroke . The PD Society Brain Bank criteria require slowness of movement (bradykinesia) plus either rigidity , resting tremor , or postural instability . Other possible causes of these symptoms need to be ruled out . Finally , three or more of the following features are required during onset or evolution : unilateral onset , tremor at rest , progression in time , asymmetry of motor symptoms , response to levodopa for at least five years , clinical course of at least ten years and appearance of dyskinesias induced by the intake of excessive levodopa . Accuracy of diagnostic criteria evaluated at autopsy is 75 ? 90 % , with specialists such as neurologists having the highest rates .

Computed tomography (CT) and conventional magnetic resonance imaging (MRI) brain scans of people with PD usually appear normal . These techniques are nevertheless useful to rule out other diseases that can be secondary causes of parkinsonism , such as basal ganglia tumors , vascular pathology and hydrocephalus . A specific technique of MRI , diffusion MRI , has been reported to be useful at discriminating between typical and atypical parkinsonism , although its exact diagnostic value is still under investigation . Dopaminergic function in the basal ganglia can be measured with different PET and SPECT radiotracers . Examples are ioflupane (¹²³I) (trade name DaTSCAN) and iometopane (Dopascan) for SPECT or fluorodeoxyglucose (¹⁸F) and DTBZ for PET . A pattern of reduced dopaminergic activity in the basal ganglia can aid in diagnosing PD .

= = Prevention = =

Exercise in middle age reduces the risk of Parkinson 's disease later in life . Caffeine also appears protective with a greater decrease in risk occurring with a larger intake of caffeinated beverages such as coffee . Although tobacco smoke causes adverse health effects , decreases life expectancy and quality of life , it may reduce the risk of PD by a third when compared to non @-@ smokers . The basis for this effect is not known , but possibilities include an effect of nicotine as a dopamine stimulant . Tobacco smoke contains compounds that act as MAO inhibitors that also might contribute to this effect .

Antioxidants , such as vitamins C and D , have been proposed to protect against the disease but

results of studies have been contradictory and no positive effect has been proven . The results regarding fat and fatty acids have been contradictory , with various studies reporting protective effects , risk @-@ increasing effects or no effects . Also , there have been preliminary indications of a possible protective role of estrogens and anti @-@ inflammatory drugs .

= = Management = =

There is no cure for Parkinson 's disease , but medications , surgery , and multidisciplinary management can provide relief from the symptoms . The main families of drugs useful for treating motor symptoms are levodopa (usually combined with a dopa decarboxylase inhibitor or COMT inhibitor which does not cross the blood ? brain barrier) , dopamine agonists and MAO @-@ B inhibitors . The stage of the disease determines which group is most useful . Two stages are usually distinguished : an initial stage in which the individual with PD has already developed some disability for which he needs pharmacological treatment , then a second stage in which an individual develops motor complications related to levodopa usage . Treatment in the initial stage aims for an optimal tradeoff between good symptom control and side @-@ effects resulting from improvement of dopaminergic function . The start of levodopa (or L @-@ DOPA) treatment may be delayed by using other medications such as MAO @-@ B inhibitors and dopamine agonists , in the hope of delaying the onset of dyskinesias . In the second stage the aim is to reduce symptoms while controlling fluctuations of the response to medication . Sudden withdrawals from medication or overuse have to be managed . When medications are not enough to control symptoms , surgery , and deep brain stimulation can be of use . In the final stages of the disease , palliative care is provided to improve quality of life .

= = = Levodopa = = =

Levodopa has been the most widely used treatment for over 30 years . L @-@ DOPA is converted into dopamine in the dopaminergic neurons by dopa decarboxylase . Since motor symptoms are produced by a lack of dopamine in the substantia nigra , the administration of L @-@ DOPA temporarily diminishes the motor symptoms .

Only 5 ? 10 % of L @-@ DOPA crosses the blood ? brain barrier . The remainder is often metabolized to dopamine elsewhere , causing a variety of side effects including nausea , dyskinesias and joint stiffness . Carbidopa and benserazide are peripheral dopa decarboxylase inhibitors , which help to prevent the metabolism of L @-@ DOPA before it reaches the dopaminergic neurons , therefore reducing side effects and increasing bioavailability . They are generally given as combination preparations with levodopa . Existing preparations are carbidopa / levodopa (co @-@ careldopa) and benserazide / levodopa (co @-@ beneldopa) . Levodopa has been related to dopamine dysregulation syndrome , which is a compulsive overuse of the medication , and punding . There are controlled release versions of levodopa in the form intravenous and intestinal infusions that spread out the effect of the medication . These slow @-@ release levodopa preparations have not shown an increased control of motor symptoms or motor complications when compared to immediate release preparations .

Tolcapone inhibits the COMT enzyme , which degrades dopamine , thereby prolonging the effects of levodopa . It has been used to complement levodopa ; however , its usefulness is limited by possible side effects such as liver damage . A similarly effective drug , entacapone , has not been shown to cause significant alterations of liver function . Licensed preparations of entacapone contain entacapone alone or in combination with carbidopa and levodopa .

Levodopa preparations lead in the long term to the development of motor complications characterized by involuntary movements called dyskinesias and fluctuations in the response to medication . When this occurs a person with PD can change from phases with good response to medication and few symptoms (" on " state) , to phases with no response to medication and significant motor symptoms (" off " state) . For this reason , levodopa doses are kept as low as possible while maintaining functionality . Delaying the initiation of therapy with levodopa by using

alternatives (dopamine agonists and MAO @-@ B inhibitors) is common practice . A former strategy to reduce motor complications was to withdraw L @-@ DOPA medication for some time . This is discouraged now since it can bring dangerous side effects such as neuroleptic malignant syndrome . Most people with PD will eventually need levodopa and later develop motor side effects .

== = Dopamine agonists == =

Several dopamine agonists that bind to dopaminergic post @-@ synaptic receptors in the brain have similar effects to levodopa . These were initially used for individuals experiencing on @-@ off fluctuations and dyskinesias as a complementary therapy to levodopa ; they are now mainly used on their own as an initial therapy for motor symptoms with the aim of delaying motor complications . When used in late PD they are useful at reducing the off periods . Dopamine agonists include bromocriptine , pergolide , pramipexole , ropinirole , piribedil , cabergoline , apomorphine and lisuride .

Dopamine agonists produce significant , although usually mild , side effects including drowsiness , hallucinations , insomnia , nausea , and constipation . Sometimes side effects appear even at a minimal clinically effective dose , leading the physician to search for a different drug . Compared with levodopa , dopamine agonists may delay motor complications of medication use but are less effective at controlling symptoms . Nevertheless , they are usually effective enough to manage symptoms in the initial years . They tend to be more expensive than levodopa . Dyskinesias due to dopamine agonists are rare in younger people who have PD , but along with other side effects , become more common with age at onset . Thus dopamine agonists are the preferred initial treatment for earlier onset , as opposed to levodopa in later onset . Agonists have been related to impulse control disorders (such as compulsive sexual activity and eating , and pathological gambling and shopping) even more strongly than levodopa .

Apomorphine , a non @-@ orally administered dopamine agonist , may be used to reduce off periods and dyskinesia in late PD . It is administered by intermittent injections or continuous subcutaneous infusions . Since secondary effects such as confusion and hallucinations are common , individuals receiving apomorphine treatment should be closely monitored . Two dopamine agonists that are administered through skin patches (lisuride and rotigotine) and are useful for people in the initial stages and possibly to control off states in those in the advanced state .

== = MAO @-@ B inhibitors == =

MAO @-@ B inhibitors (safinamide , selegiline and rasagiline) increase the level of dopamine in the basal ganglia by blocking its metabolism . They inhibit monoamine oxidase B (MAO @-@ B) which breaks down dopamine secreted by the dopaminergic neurons . The reduction in MAO @-@ B activity results in increased L @-@ DOPA in the striatum . Like dopamine agonists , MAO @-@ B inhibitors used as monotherapy improve motor symptoms and delay the need for levodopa in early disease , but produce more adverse effects and are less effective than levodopa . There are few studies of their effectiveness in the advanced stage , although results suggest that they are useful to reduce fluctuations between on and off periods . An initial study indicated that selegiline in combination with levodopa increased the risk of death , but this was later disproven .

== = Other drugs == =

Other drugs such as amantadine and anticholinergics may be useful as treatment of motor symptoms . However , the evidence supporting them lacks quality , so they are not first choice treatments . In addition to motor symptoms , PD is accompanied by a diverse range of symptoms . A number of drugs have been used to treat some of these problems . Examples are the use of quetiapine for psychosis , cholinesterase inhibitors for dementia , and modafinil for daytime sleepiness . A 2010 meta @-@ analysis found that non @-@ steroidal anti @-@ inflammatory

drugs (apart from aspirin) , have been associated with at least a 15 percent (higher in long @-@ term and regular users) reduction of incidence of the development of Parkinson 's disease .

= = = Surgery = = =

Treating motor symptoms with surgery was once a common practice , but since the discovery of levodopa , the number of operations declined . Studies in the past few decades have led to great improvements in surgical techniques , so that surgery is again being used in people with advanced PD for whom drug therapy is no longer sufficient . Surgery for PD can be divided in two main groups : lesional and deep brain stimulation (DBS) . Target areas for DBS or lesions include the thalamus , the globus pallidus or the subthalamic nucleus . Deep brain stimulation (DBS) is the most commonly used surgical treatment , developed in the 1980s by Alim @-@ Louis Benabid and others . It involves the implantation of a medical device called a neurostimulator which sends electrical impulses to specific parts of the brain . DBS is recommended for people who have PD with motor fluctuations and tremor inadequately controlled by medication , or to those who are intolerant to medication , as long as they do not have severe neuropsychiatric problems . Other , less common , surgical therapies involve intentional formation of lesions to suppress overactivity of specific subcortical areas . For example , pallidotomy involves surgical destruction of the globus pallidus to control dyskinesia .

= = = Rehabilitation = = =

Exercise programs are recommended in people with Parkinson 's disease . There is some evidence that speech or mobility problems can improve with rehabilitation , although studies are scarce and of low quality . Regular physical exercise with or without physiotherapy can be beneficial to maintain and improve mobility , flexibility , strength , gait speed , and quality of life . When an exercise program is performed under the supervision of a physiotherapist , there are more improvements in motor symptoms , mental and emotional functions , daily living activities , and quality of life compared to a self @-@ supervised exercise program at home . In terms of improving flexibility and range of motion for people experiencing rigidity , generalized relaxation techniques such as gentle rocking have been found to decrease excessive muscle tension . Other effective techniques to promote relaxation include slow rotational movements of the extremities and trunk , rhythmic initiation , diaphragmatic breathing , and meditation techniques . As for gait and addressing the challenges associated with the disease such as hypokinesia (slowness of movement) , shuffling and decreased arm swing ; physiotherapists have a variety of strategies to improve functional mobility and safety . Areas of interest with respect to gait during rehabilitation programs focus on but are not limited to improving gait speed , the base of support , stride length , trunk and arm swing movement . Strategies include utilizing assistive equipment (pole walking and treadmill walking) , verbal cueing (manual , visual and auditory) , exercises (marching and PNF patterns) and altering environments (surfaces , inputs , open vs. closed) . Strengthening exercises have shown improvements in strength and motor function for people with primary muscular weakness and weakness related to inactivity with mild to moderate Parkinson 's disease . However , reports show a significant interaction between strength and the time the medications was taken . Therefore , it is recommended that people with PD should perform exercises 45 minutes to one hour after medications when they are at their best . Also , due to the forward flexed posture , and respiratory dysfunctions in advanced Parkinson 's disease , deep diaphragmatic breathing exercises are beneficial in improving chest wall mobility and vital capacity . Exercise may improve constipation .

One of the most widely practiced treatments for speech disorders associated with Parkinson 's disease is the Lee Silverman voice treatment (LSVT) . Speech therapy and specifically LSVT may improve speech . Occupational therapy (OT) aims to promote health and quality of life by helping people with the disease to participate in as many of their daily living activities as possible . There have been few studies on the effectiveness of OT and their quality is poor , although there is some indication that it may improve motor skills and quality of life for the duration of the therapy .

== Palliative care ==

Palliative care is specialized medical care for people with serious illnesses, including Parkinson's. The goal of this speciality is to improve quality of life for both the person suffering from Parkinson's and the family by providing relief from the symptoms, pain, and stress of illnesses. As Parkinson's is not a curable disease, all treatments are focused on slowing decline and improving quality of life, and are therefore palliative in nature.

Palliative care should be involved earlier, rather than later in the disease course. Palliative care specialists can help with physical symptoms, emotional factors such as loss of function and jobs, depression, fear, and existential concerns.

Along with offering emotional support to both the patient and family, palliative care serves an important role in addressing goals of care. People with Parkinson's may have many difficult decisions to make as the disease progresses such as wishes for feeding tube, non-invasive ventilator, and tracheostomy; wishes for or against cardiopulmonary resuscitation; and when to use hospice care. Palliative care team members can help answer questions and guide people with Parkinson's on these complex and emotional topics to help them make the best decision based on their own values.

== Other treatments ==

Muscles and nerves that control the digestive process may be affected by PD, resulting in constipation and gastroparesis (food remaining in the stomach for a longer period than normal). A balanced diet, based on periodical nutritional assessments, is recommended and should be designed to avoid weight loss or gain and minimize consequences of gastrointestinal dysfunction. As the disease advances, swallowing difficulties (dysphagia) may appear. In such cases it may be helpful to use thickening agents for liquid intake and an upright posture when eating, both measures reducing the risk of choking. Gastrostomy to deliver food directly into the stomach is possible in severe cases.

Levodopa and proteins use the same transportation system in the intestine and the blood-brain barrier, thereby competing for access. When they are taken together, this results in a reduced effectiveness of the drug. Therefore, when levodopa is introduced, excessive protein consumption is discouraged and well-balanced Mediterranean diet is recommended. In advanced stages, additional intake of low-protein products such as bread or pasta is recommended for similar reasons. To minimize interaction with proteins, levodopa should be taken 30 minutes before meals. At the same time, regimens for PD restrict proteins during breakfast and lunch, allowing protein intake in the evening.

Repetitive transcranial magnetic stimulation temporarily improves levodopa-induced dyskinesias. Its usefulness in PD is an open research topic, although recent studies have shown no effect by rTMS. Several nutrients have been proposed as possible treatments; however there is no evidence that vitamins or food additives improve symptoms. There is no evidence to substantiate that acupuncture and practice of Qigong, or Tai chi, have any effect on the course of the disease or symptoms. Further research on the viability of Tai chi for balance or motor skills are necessary. Fava beans and velvet beans are natural sources of levodopa and are eaten by many people with PD. While they have shown some effectiveness in clinical trials, their intake is not free of risks. Life-threatening adverse reactions have been described, such as the neuroleptic malignant syndrome.

== Prognosis ==

PD invariably progresses with time. A severity rating method known as the Unified Parkinson's Disease Rating Scale (UPDRS) is the most commonly used metric for clinical study. A modified version known as the MDS-UPDRS is also sometimes used. An older scaling method known

as the Hoehn and Yahr scale (originally published in 1967) , and a similar scale known as the Modified Hoehn and Yahr scale , have also been commonly used . The Hoehn and Yahr scale defines five basic stages of progression .

Motor symptoms , if not treated , advance aggressively in the early stages of the disease and more slowly later . Untreated , individuals are expected to lose independent ambulation after an average of eight years and be bedridden after ten years . However , it is uncommon to find untreated people nowadays . Medication has improved the prognosis of motor symptoms , while at the same time it is a new source of disability because of the undesired effects of levodopa after years of use . In people taking levodopa , the progression time of symptoms to a stage of high dependency from caregivers may be over 15 years . However , it is hard to predict what course the disease will take for a given individual . Age is the best predictor of disease progression . The rate of motor decline is greater in those with less impairment at the time of diagnosis , while cognitive impairment is more frequent in those who are over 70 years of age at symptom onset .

Since current therapies improve motor symptoms , disability at present is mainly related to non-motor features of the disease . Nevertheless , the relationship between disease progression and disability is not linear . Disability is initially related to motor symptoms . As the disease advances , disability is more related to motor symptoms that do not respond adequately to medication , such as swallowing / speech difficulties , and gait / balance problems ; and also to motor complications , which appear in up to 50 % of individuals after 5 years of levodopa usage . Finally , after ten years most people with the disease have autonomic disturbances , sleep problems , mood alterations and cognitive decline . All of these symptoms , especially cognitive decline , greatly increase disability .

The life expectancy of people with PD is reduced . Mortality ratios are around twice those of unaffected people . Cognitive decline and dementia , old age at onset , a more advanced disease state and presence of swallowing problems are all mortality risk factors . On the other hand , a disease pattern mainly characterized by tremor as opposed to rigidity predicts an improved survival . Death from aspiration pneumonia is twice as common in individuals with PD as in the healthy population .

In 2013 PD resulted in about 103 000 deaths globally , up from 44 000 deaths in 1990 . The death rate increased from an average of 1 @ 5 to 1 @ 8 per 100 000 during that time .

= = Epidemiology = =

PD is the second most common neurodegenerative disorder after Alzheimer 's disease and affects approximately seven million people globally and one million people in the United States . The proportion in a population at a given time is about 0 @ 3 % in industrialized countries . PD is more common in the elderly and rates rises from 1 % in those over 60 years of age to 4 % of the population over 80 . The mean age of onset is around 60 years , although 5 ? 10 % of cases , classified as young onset PD , begin between the ages of 20 and 50 . PD may be less prevalent in those of African and Asian ancestry , although this finding is disputed . Some studies have proposed that it is more common in men than women , but others failed to detect any differences between the two sexes . The number of new cases per year of PD is between 8 and 18 per 100 000 person ? years .

Many risk factors and protective factors have been proposed , sometimes in relation to theories concerning possible mechanisms of the disease , however , none have been conclusively related to PD by empirical evidence . When epidemiological studies have been carried out in order to test the relationship between a given factor and PD , they have often been flawed and their results have in some cases been contradictory . The most frequently replicated relationships are an increased risk of PD in those exposed to pesticides , and a reduced risk in smokers .

= = History = =

Several early sources , including an Egyptian papyrus , an Ayurvedic medical treatise , the Bible ,

and Galen 's writings , describe symptoms resembling those of PD . After Galen there are no references unambiguously related to PD until the 17th century . In the 17th and 18th centuries , several authors wrote about elements of the disease , including Sylvius , Gaubius , Hunter and Chomel .

In 1817 an English doctor , James Parkinson , published his essay reporting six cases of paralysis agitans . An Essay on the Shaking Palsy described the characteristic resting tremor , abnormal posture and gait , paralysis and diminished muscle strength , and the way that the disease progresses over time . Early neurologists who made further additions to the knowledge of the disease include Trousseau , Gowers , Kinnier Wilson and Erb , and most notably Jean @-@ Martin Charcot , whose studies between 1868 and 1881 were a landmark in the understanding of the disease . Among other advances , he made the distinction between rigidity , weakness and bradykinesia . He also championed the renaming of the disease in honor of James Parkinson .

In 1912 Frederic Lewy described microscopic particles in affected brains , later named " Lewy bodies " . In 1919 Konstantin Tretiakoff reported that the substantia nigra was the main cerebral structure affected , but this finding was not widely accepted until it was confirmed by further studies published by Rolf Hassler in 1938 . The underlying biochemical changes in the brain were identified in the 1950s , due largely to the work of Arvid Carlsson on the neurotransmitter dopamine and Oleh Hornykiewicz on its role on PD . In 1997 , alpha @-@ synuclein was found to be the main component of Lewy bodies by Spillantini , Trojanowski , Goedert and others .

Anticholinergics and surgery (lesioning of the corticospinal pathway or some of the basal ganglia structures) were the only treatments until the arrival of levodopa , which reduced their use dramatically . Levodopa was first synthesized in 1911 by Casimir Funk , but it received little attention until the mid 20th century . It entered clinical practice in 1967 and brought about a revolution in the management of PD . By the late 1980s deep brain stimulation introduced by Alim @-@ Louis Benabid and colleagues at Grenoble , France , emerged as a possible treatment .

= = Society and culture = =

= = = Cost = = =

The costs of PD to society are high , but precise calculations are difficult due to methodological issues in research and differences between countries . The annual cost in the UK is estimated to be between 449 million and 3 @.@ 3 billion pounds , while the cost per patient per year in the U.S. is probably around \$ 10 @,@ 000 and the total burden around 23 billion dollars . The largest share of direct cost comes from inpatient care and nursing homes , while the share coming from medication is substantially lower . Indirect costs are high , due to reduced productivity and the burden on caregivers . In addition to economic costs , PD reduces quality of life of those with the disease and their caregivers .

= = = Advocacy = = =

11 April , the birthday of James Parkinson , has been designated as World Parkinson 's Day . A red tulip was chosen by international organizations as the symbol of the disease in 2005 : it represents the James Parkinson Tulip cultivar , registered in 1981 by a Dutch horticulturalist . Advocacy organizations include the National Parkinson Foundation , which has provided more than \$ 180 million in care , research and support services since 1982 , Parkinson 's Disease Foundation , which has distributed more than \$ 115 million for research and nearly \$ 50 million for education and advocacy programs since its founding in 1957 by William Black ; the American Parkinson Disease Association , founded in 1961 ; and the European Parkinson 's Disease Association , founded in 1992 .

= = = Notable cases = = =

Actor Michael J. Fox has PD and has greatly increased the public awareness of the disease . After diagnosis , Fox embraced his Parkinson 's in television roles , sometimes acting without medication , in order to further illustrate the effects of the condition . He has written two autobiographies in which his fight against the disease plays a major role , and appeared before the United States Congress without medication to illustrate the effects of the disease . The Michael J. Fox Foundation aims to develop a cure for Parkinson 's disease . Fox received an honorary doctorate in medicine from Karolinska Institutet for his contributions to research in Parkinson 's disease .

Professional cyclist and Olympic medalist Davis Phinney , who was diagnosed with young onset Parkinson 's at age 40 , started the Davis Phinney Foundation in 2004 to support Parkinson 's research , focusing on quality of life for people with the disease .

Muhammad Ali showed signs of Parkinson 's when he was 38 , but was not diagnosed until he was 42 , and has been called the " world 's most famous Parkinson 's patient " . Whether he had PD or a parkinsonism related to boxing is unresolved .

= = Research = =

There is little prospect of significant new PD treatments in the near future . Currently active research directions include the search for new animal models of the disease and studies of the potential usefulness of gene therapy , stem cell transplants and neuroprotective agents .

= = = Animal models = = =

PD is not known to occur naturally in any species other than humans , although animal models which show some features of the disease are used in research . The appearance of parkinsonian symptoms in a group of drug addicts in the early 1980s who consumed a contaminated batch of the synthetic opiate MPPP led to the discovery of the chemical MPTP as an agent that causes a parkinsonian syndrome in non @-@ human primates as well as in humans . Other predominant toxin @-@ based models employ the insecticide rotenone , the herbicide paraquat and the fungicide maneb . Models based on toxins are most commonly used in primates . Transgenic rodent models that replicate various aspects of PD have been developed . Using the neurotoxin 6 @-@ hydroxydopamine , also known as 6 @-@ OHDA , it creates a model of Parkinson 's disease in rats by targeting and destroying dopaminergic neurons in the nigrostriatal pathway when injected into the substantia nigra .

= = = Gene therapy = = =

Gene therapy typically involves the use of a non @-@ infectious virus (i.e. , a viral vector such as the adeno @-@ associated virus) to shuttle genetic material into a part of the brain . The gene used leads to the production of an enzyme that helps to manage PD symptoms or protects the brain from further damage . In 2010 there were four clinical trials using gene therapy in PD . There have not been important adverse effects in these trials although the clinical usefulness of gene therapy is still unknown . One of these reported positive results in 2011 , but the company filed for bankruptcy in March 2012 .

= = = Neuroprotective treatments = = =

Investigations on neuroprotection are at the forefront of PD research . Several molecules have been proposed as potential treatments . However , none of them have been conclusively demonstrated to reduce degeneration . Agents currently under investigation include anti @-@ apoptotics (omigapil , CEP @-@ 1347) , antiglutamatergics , monoamine oxidase inhibitors (selegiline , rasagiline) , promitochondrials (coenzyme Q10 , creatine) , calcium channel blockers (isradipine) and growth factors (GDNF) . Preclinical research also targets alpha @-@ synuclein . A

vaccine that primes the human immune system to destroy alpha @-@ synuclein , PD01A (developed by Austrian company , Affiris) , has entered clinical trials in humans .

= = = Neural transplantation = = =

Since early in the 1980s , fetal , porcine , carotid or retinal tissues have been used in cell transplants , in which dissociated cells are injected into the substantia nigra in the hope that they will incorporate themselves into the brain in a way that replaces the dopamine @-@ producing cells that have been lost . Although there was initial evidence of mesencephalic dopamine @-@ producing cell transplants being beneficial , double @-@ blind trials to date indicate that cell transplants produce no long @-@ term benefit . An additional significant problem was the excess release of dopamine by the transplanted tissue , leading to dystonias . Stem cell transplants are a recent research target , because stem cells are easy to manipulate and stem cells transplanted into the brains of rodents and monkeys have been found to survive and reduce behavioral abnormalities . Nevertheless , use of fetal stem cells is controversial . It has been proposed that effective treatments may be developed in a less controversial way by use of induced pluripotent stem cells taken from adults .