Parkinson's Disease: An Overview of Etiology, Clinical Manifestations, and Treatment

Arif Dalvi, Kelly E. Lyons, and Rajesh Pahwa

Parkinson syndrome is an umbrella term grouping together clinical syndromes that share the cardinal symptoms of bradykinesia, rigidity, and rest tremor. By far the largest occupant of this umbrella is idiopathic Parkinson's disease (PD), with degeneration of the nigrostriatal dopaminergic system and the presence of Lewy bodies in the substantia nigra as its pathological hallmarks [1].

A number of other neurodegenerative diseases share this space with distinct clinical features and pathological mechanisms. The combination of the cardinal features of Parkinson syndrome with additional manifestations such as ophthalmoplegia, dysautonomia, cortical and cerebellar signs, or dementia is referred to by the rubric parkinson-plus syndrome that includes disorders such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB). Other well-defined heredodegenerative diseases such as Wilson's disease and Huntington's disease can also mimic PD. Finally, structural lesions in the brain such as normal pressure hydrocephalus and small vessel ischemic disease can resemble PD [2].

Clinical Features

The diagnosis of PD is primarily based on clinical criteria. The United Kingdom Parkinson's Disease Society Brain Bank criteria are most often used, with positive diagnostic features including the presence of bradykinesia, and at least one of muscular rigidity, tremor at rest, or postural instability not explained by other etiologies.

A. Dalvi, M.D., M.B.A. (✉)
Parkinson's Disease and Movement Disorders Program, Methodist Hospital Neuroscience Institute, Merrillville, IN, USA
e-mail: dalvi.md@gmail.com

K.E. Lyons, Ph.D. • R. Pahwa, M.D.
Department of Neurology, University of Kansas Medical Center, Kansas City, KS, USA

M. Thomas (ed.), *Inflammation in Parkinson's Disease: Scientific and Clinical Aspects*,
DOI 10.1007/978-3-319-08046-8_1,

Exclusionary criteria include history of strokes, repeated head injury, or definite encephalitis, oculogyric crisis, neuroleptic treatment at symptom onset, sustained remission, unilateral symptoms after 3 years, supranuclear gaze palsy, cerebellar signs, early, severe autonomic features or dementia, Babinski sign, cerebral tumor or hydrocephalus, or no response to high doses of levodopa. Supportive features include at least three of the following: unilateral onset, rest tremor, progression, persistent asymmetry with side of onset most affected, good response to levodopa, levodopa-induced dyskinesia, and clinical course of at least 10 years [3].

The clinical syndrome of PD is not limited to these cardinal symptoms. Other motor manifestations include postural instability, stooped posture, a shuffling, festinating or freezing gait, and dystonic posturing, particularly in the lower extremities. In addition, long-term treatment, particularly with levodopa is associated with the development of dyskinesia and a fluctuating response to medical treatment described as the "on–off" phenomenon [4].

There is an increasing recognition of non-motor symptoms in PD, some of which may precede the onset of motor symptoms by many decades. An altered sense of smell and constipation can occur in PD and have also been examined as potential predictors of the onset of PD. Depression and anxiety are common comorbid symptoms. Changes in the sleep–wake cycle and REM behavior disorder may also be seen. Dysautonomia usually becomes more prominent in the later stages of the disease, unlike in MSA, where it may be a presenting feature. Autonomic symptoms include orthostatic hypotension, urinary frequency and incontinence, delayed gastric emptying and sialorrhea, erectile dysfunction, and loss of libido [5]. Dementia is part of the natural history of PD, although, in contrast to DLB, it occurs relatively late in the course. A global dementia, such as is seen in Alzheimer's disease, is less commonly observed. Instead an executive dysfunction is seen with retrieval being affected more than memory and short-term memory loss more common than that of long-term memory. Long-standing PD may also be complicated by the development of hallucinations and psychosis [6].

Laboratory Studies

The diagnosis of PD remains a clinical diagnosis. However, judicious use of imaging and laboratory studies helps exclude diseases that may resemble PD but have a significantly different treatment and prognosis. In younger patients it is important to screen for Wilson's disease with serum ceruloplasmin, 24-h urine copper, and liver function studies. Imaging studies in the form of CT or MRI of the brain help rule out structural etiologies such as normal pressure hydrocephalus and vascular parkinsonism. Brain MRI also detects changes in the basal ganglia or thalamus in Wilson's disease and may reveal caudate atrophy in Huntington's disease [1].

Where diagnostic uncertainty exists, for example, between essential tremor (ET) and PD, the use of DaTscan SPECT imaging can be useful. Dopamine transporter (DaT) levels in the striatum are lower in parkinsonism due to loss of dopaminergic

cells but are normal in other etiologies of tremor such as ET. Labeling the dopamine transporter with ioflupane (a radioactive iodine-labeled cocaine derivative) and measuring the levels with SPECT imaging can help distinguish ET from parkinsonism including PD. It is important to note that DaTscan is unable to distinguish PD from other forms of parkinsonism [7].

Etiology of PD

In his seminal *An Essay on the Shaking Palsy* Sir James Parkinson considered "indulgence in spirituous liquors" and "long lying on the damp ground" as possible etiologies of PD [8]. Seventy years later Gower reported that about 15 % of his patients with PD had a family history [9]. A twin study on WWII veterans showed genetic factors in patients with typical or older age of onset played a lesser role, as similar concordance rates were observed in monozygotic and dizygotic twins. In contrast, in patients with an onset prior to age 50, there was a more substantial genetic contribution [10]. Following the discovery of the α-synuclein (SNCA) gene [11] and the subsequent discovery of a number of additional PARK genes the debate between supporters of genetic and environmental causes has been renewed. The assumptions of Parkinson regarding the etiology of PD have not held up, but a number of alternative environmental factors have been proposed. Current understanding of the etiology of PD points to a multifactorial disorder with gene–environment interactions leading to neuronal cell death (Fig. 1).

Selective Vulnerability of the Nigrostriatal Tract

The reason for selective vulnerability of the substantia nigra pars compacta (SNc) in the pathogenesis of PD is an area of active study. A number of hypotheses have been proposed as an explanation. Oxidative stress involving mitochondrial dysfunction may be more prominent in the SNc relative to other brain regions, primarily due to reactive oxygen species produced during dopamine storage and breakdown [12]. Models of endoplasmic reticulum stress show age-dependent selective vulnerability of dopaminergic neurons, also related to the oxidative by-products of dopamine metabolism. Dopamine metabolites, especially the monoamine oxidase (MAO) metabolite 3,4-dihydroxyphenylacetaldehyde (DOPAL), can trigger SNCA aggregation in SNc neurons [13].

Accumulation of SNCA in cultured human dopaminergic neurons results in apoptotic cell death. This mechanism requires endogenous dopamine production and is mediated by reactive oxygen species. In contrast, SNCA is neuroprotective in non-dopaminergic human cortical neurons. Thus, accumulation of soluble SNCA protein complexes can render endogenous dopamine toxic, suggesting a potential

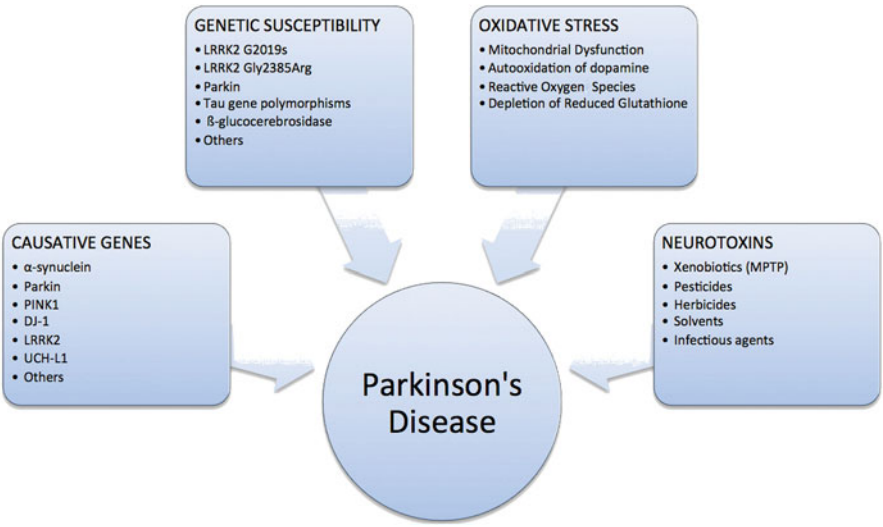

Fig. 1 The multifactorial etiology of Parkinson's disease. Causative genes and genetic susceptibility factors interact with environmental triggers and endogenous causes of oxidative stress. Misfolding and aggregation of proteins together with mitochondrial dysfunction provide the framework for neuronal cell death leading to Parkinson's disease. © Arif Dalvi 2007. Reprinted from Dalvi A, Walsh R. Etiology of Parkinson's disease. In: Simuni T, Pahwa R, editors. Parkinson's Disease. New York: Oxford University Press; 2009: 51–62, Figure 5.1. By permission of Oxford University Press, USA

mechanism for the selectivity of neuronal loss in PD [14]. Inflammatory mechanisms may also play a role, especially in the context of activated microglial cells. Patients with PD have selective degeneration of neurons in the SNc accompanied by microglial activation and a challenged immune system [15].

Environmental Factors

Environmental factors have always been considered to play a significant role in the etiology of PD. One of the most commonly identified is exposure to herbicides and pesticides. In a multifactorial model based on a study of rural populations, years of rural living and groundwater use were predictive of PD. Pesticide exposure was found to be a risk factor independent of rural living [16]. However, not all studies support rural living as a risk factor. In China drinking well water was associated with a reduced risk of PD, while living in proximity to rubber plants or drinking river water was associated with a higher risk [17]. In a large serial cross-sectional study of Medicare beneficiaries, two geographic belts with high predisposition to PD were found. This series of over 450,000 PD cases revealed a higher concentration of PD cases in the Midwest and Northeast regions. Prevalence in urban counties

was greater than in rural ones [18]. Epidemiologic studies investigating potential links between solvents and PD have yielded mostly null or weak associations [19]. However, a study of 99 twin pairs from the World War II Veterans Twin Cohort suggested possible etiologic relations with trichloroethylene (TCE) and other chlorinated solvents, although the sample size was small and dose–response gradients were not observed. It should be noted that TCE is the most common organic contaminant in groundwater [20]. Welding and manganese exposure have been suggested as risk factors for PD [21]. However, a meta-analysis that pooled data from 13 studies for welding and 3 studies for manganese exposure failed to support this hypothesis [22].

Genetic Factors

A first-degree relative of an affected individual is approximately twice as likely to develop PD compared to someone with no family history of PD [23]. While concordance rates in monozygotic and dizygotic twins are equal in late-onset PD, they are much higher in monozygotic (~100 %) than in dizygotic twins (~17 %) in early-onset PD, consistent with early-onset PD having a strong genetic determinant [24]. Several genes have been definitively linked with familial PD, along with other candidate genes whose association with PD is less established.

α-Synuclein

Three mutations of this gene as well as duplication and triplication of the gene region have been described in familial PD. The pathological role of SNCA in PD is also not definitively known, but SNCA is a major component of Lewy bodies observed in post-mortem studies of PD brains [12]. Autosomal-dominant inheritance of familial PD is observed with mutations of α-synuclein. The clinical course of affected individuals is similar to sporadic PD, but with an earlier mean age of onset, higher rate of dementia, and some neuropathological features not common in sporadic PD including more tau-positive extra-perikaryal spheroid-like and thread-like lesions and more marked neuronal loss. The physiological role of SNCA is unclear, but it may be involved in synaptic vesicle recycling particularly involving dopamine storage [25].

Parkin

This gene is the most common autosomal-recessive PD gene mutation, and a wide variety of parkin mutations have been found in familial PD. Parkin is mutated in ~50 % of autosomal-recessive early-onset PD and in ~70 % of juvenile PD with

onset less than 20 years. The clinical course of affected individuals is typically characterized by early onset, slow progression, and good response to dopamine [26]. The physiological role of parkin is thought to relate to its function as an ubiquitin ligase important in normal cellular protein degradation pathways. Deficiency in this function may underlie the pathology associated with mutant parkin, including possible disruption of microtubule and mitochondrial function, proteasomal degradation, and neuroprotection [27].

PINK1

Mutations of this gene are thought to result in loss of kinase function consistent with the observed autosomal-recessive inheritance pattern. The clinical course in affected individuals typically demonstrates disease onset at less than 50 years with otherwise mostly classical features of sporadic PD [28]. The physiological role of PINK1 is thought to involve regulation of the electron transport chain and maintenance of mitochondrial membrane potential, and the pathology resulting from mutations of PINK1 may relate to mitochondrial dysfunction in response to oxidative stress, possibly involving parkin [29].

DJ-1

Multiple types of DJ-1 mutations have been identified, and inheritance is autosomal-recessive. Affected individuals typically have age of onset around 20–40 years with mostly classical Parkinsonian symptoms and usually respond well to dopaminergic therapy. Focal dystonia and blepharospasm may present early in the course of the disease [30]. DJ-1 is thought to play a role as an antioxidant and sensor of oxidative stress, but may also be involved in protein degradation pathways and apoptotic signaling possibly in conjunction with parkin and PINK1. Furthermore, dysfunction of DJ-1 may affect these pathways in a manner that preferentially involves dopaminergic neurons [31].

LRRK2

LRRK2 mutations are found throughout this gene's functional domains with the most common mutant being relatively frequent in both familial autosomal-dominant PD (~4 %) and in sporadic PD (~1 %) [32]. In certain populations, such as North African Arabs and Ashkenazi Jews, the prevalence of LRRK2 mutations may account for up to 40 % of all PD cases [33, 34]. LRRK2 mutations result in parkinsonism very similar to classical PD, and penetrance of symptoms is very tightly linked with aging, also similar to idiopathic PD. Despite the relatively uniform

classic parkinsonism seen with LRRK2 mutations, the neuropathology is quite diverse suggesting that LRRK2 dysfunction may be important in the initiation of altered function of multiple cellular systems with a final common pathway resulting in dopaminergic cell death [35]. The physiologic role of LRRK2 is thought to involve its putative kinase and GTPase activity, and mutant forms have shown increased kinase activity consistent with a gain of function seen often in autosomal-dominant diseases [36]. PD-causing LRRK2 mutations deregulate the autophagy–lysosomal pathway. G2019S mutant LRRK2 can lead to abnormal accumulation of autophagic and lysosomal structures in primary cortical neurons and neuronal cell lines in culture [37].

UCH-L1

It is unclear if mutations of UCH-L1 identified in several families are truly involved in PD due to the failure of the mutation to segregate with disease in one family and the failure of other mutations to be identified despite extensive screening [38]. It is intriguing, however, that a polymorphism in this gene may protect against development of PD, possibly through alteration of interaction of UCH-L1 with SNCA [39]. UCH-L1 accumulation is likely to play a pathological role in inclusion formation in PD through a malfunction of the ubiquitin/proteasome system that leads to an inability to clear aggresomes [40].

Gene–Environment Interactions

The ultimate etiology of PD may be based on multiple factors including genetics, environmental exposures and aging-related apoptotic processes. The complex interaction between these factors may serve as an explanation for the heterogeneity observed in clinical presentations. Various animal models have attempted to examine the interplay of these interactions.

DJ-1 mutations have been associated with autosomal-recessive early-onset PD. In a DJ-1 knockout transgenic mouse model the susceptibility of nigrostriatal deficits was found to increase following exposure to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). In addition, in wild-type mice adenoviral-mediated overexpression of DJ-1 was found to block MPTP induced neuronal loss and neurodegeneration in the substantia nigra. Thus, DJ-1 may play a significant role in the protection of neurons against oxidative stress and environmental neurotoxins [41]. Lymphoblast cells derived from DJ-1 patients display aberrant mitochondrial morphology. These DJ-1-dependent mitochondrial defects contribute to oxidative stress-induced sensitivity to cell death. The aberrant mitochondrial phenotype can be rescued by the expression of Pink1 and Parkin, two PD-linked genes involved with mitochondrial function. Thus a complex interplay between genetic factors can lead to a differential response to oxidative stress produced by environmental toxins [42].

Infectious Etiologies for PD

In 1916–1927 an epidemic of an influenza-like illness ravaged Europe and North America. Mortality was up to 40 % in those affected, and most survivors developed parkinsonism over the next 10 years [43]. The specific agent causing this pandemic of encephalitis lethargica was never isolated. However, it drew attention to an infectious etiology as a contributor to PD. Of note, the possibility that an encephalitis lethargica syndrome is still prevalent has been raised with the suggested mechanism being autoimmunity against deep grey matter neurons [44].

Antibodies to the Epstein–Barr virus have shown cross reactivity with SNCA in the brains of patients with PD [45]. Although no evidence of ongoing viral infection in PD has been reported, immunohistochemistry shows reactive microglia and activated complement components suggestive of chronic inflammation occur in affected brain regions in PD [46]. The viral hypothesis has also been invoked to explain the observation of the higher incidence of PD in teachers, medical workers, loggers, and miners [47]. In monozygotic twins discordant for PD a significantly increased risk was noted in the twin working as a teacher or health care worker [24].

PD as a Prion-Like Disease

SNCA has been determined to be the major component of Lewy bodies, which are the pathological hallmark of PD [48]. Three missense mutations in the SNCA gene have been associated with autosomal-dominant PD, and genome-wide association studies have linked single-nucleotide polymorphisms in this gene to sporadic PD [49]. The spread of SNCA pathology in the brain has been implicated in the progression of PD and in the caudal to rostral spread of Lewy bodies in PD that forms the basis of Braak staging in PD [50]. This has led to the recognition that SNCA has attributes that are common to prion-like proteins, including multiple conformations and the ability to transfer from cell to cell. The physiological form of SNCA has an unstructured α-helical conformation that changes to oligomers and fibrils rich in β-sheets in the mutant pathological form [51]. In vivo studies have also documented the ability of SNCA to transfer and propagate from cell to cell [52]. Support for the prion-like spread of PD was furthered by observations in autopsied brains of individuals who underwent embryonic stem cell implants in the 1980–1990s. Of note SNCA pathology was found not only in the patient's own brain tissue but also in the grafted neurons. These grafted neurons were found to show SNCA and ubiquitin immunoreactivity and showed the typical morphology of Lewy bodies with a dense core and a lighter halo. Given that the grafted cells were only 10–15 years old, it was felt that an independent autonomic process could not be implicated but rather the possibility of spread through a prion-like mechanism was raised [53]. However, in contrast to prion diseases like Creutzfeldt–Jakob disease there is no evidence that misfolded SNCA can be transmitted from one individual to another; thus, it is best described as a prion-like protein.

Inflammation and PD

Inflammation has been increasingly studied as part of the pathophysiology of neurodegenerative diseases. In PD an increase in microglial activation has been shown in the substantia nigra cells that may be a marker of neurotoxicity [54]. Microglia have multiple roles, including immune surveillance and mediating immune responses to pathogens by secreting cytokines, chemokines, prostaglandins, reactive oxygen and nitrogen species, and growth factors. Some of these factors have neuroprotective effects, while others enhance oxidative stress and can trigger apoptosis. Chronic neuroinflammation may reduce the levels of neuroprotective factors, increasing the vulnerability to inflammation induced cell death of substantia nigra neurons [55].

In a rat model created by injecting an adeno-associated virus vector for SNCA into the substantia nigra the control arm showed a significant loss of tyrosine hydroxylase positive (TH+) neurons. However, in rats that were fed a diet rich in spirulina, a blue-green algae, a significantly greater number of TH + cells were preserved. A neuroprotective effect from reducing the inflammatory component associated with microglial association was hypothesized as the mechanism [56]. Telmisartan, an angiotensin I receptor blocker has been shown in animal models to inhibit the microglial inflammatory response and thereby reduce dopaminergic cell death. The neuroprotective effect is believed to be mediated, at least in part, by the activation of peroxisome proliferator-activated receptor gamma (PPAR-γ) [57]. Oral antidiabetic thiazolidinediones have also been shown to exert neuroprotective effects in models of PD. Their antidiabetic effect is due to activation of PPAR-γ, and this may also reduce inflammation and apoptosis, thereby leading to a neuroprotective effect [58]. Pioglitazone and retinoic acid were tested in a rotenone-induced model of PD in rats. Rotenone significantly reduced locomotor activity of the rats and also significantly reduced dopamine levels in the striatum and hippocampus. Pioglitazone, but not retinoic acid, significantly reversed the reduced striatal dopamine level [59]. Isradipine, a dihydropyridine calcium channel blocker (DiCCB), has also been shown to be neuroprotective in preclinical models of parkinsonism. It was suggested that with increasing age, dopaminergic neurons relied more on L-type voltage-gated calcium channels with a pore-forming Cav1.3 (caveolin.3) subunit, making them more vulnerable to toxin-induced injury. Neurons of younger animals used sodium-dependent channels. If Cav1.3 channels in older animals were blocked by isradipine, their neurons reverted to the juvenile form of the channels rendering them less prone to injury [60].

Oxidative Stress and PD

The discovery that MPTP is toxic to nigral dopaminergic cells led to research into the environmental causes of PD and oxidative stress as an underlying mechanism [61]. A higher incidence of PD had been reported in those living in rural areas, and

the observation that paraquat, a weed killer, had structural resemblance to MPTP lent further credence to this hypothesis [62]. Oxidative stress remains a key concept in understanding the pathophysiology of PD [63]. It is believed that free radical production resulting from the enzymatic oxidation of dopamine as well as exposure to external toxins that cause oxidative stress play a role in the causation of the disease and disease progression [64]. In contrast, the observation of a negative correlation between plasma urate levels and disease progression in PD may represent altered antioxidant activity through reduced glutathione levels or the antioxidant and metal complexing properties of urate [65].

Both neuronal and glial sources have been implicated in oxidative stress. The most likely contributor of oxidative stress is believed to be increased free radical formation from the mitochondria. Neurotoxicity of MPTP through its metabolite MPP^+ occurs through the inhibition of complex 1 in the electron transport chain [66]. Mutations in SNCA, parkin, PINK1, DJ-1, and possibly LRRK2 have been associated with altered mitochondrial function. Thus the mitochondria may represent a common target for both genetic and environmental etiologies of PD [67].

Mechanism of Action of PD Medications

Arvid Carlsson in 1957 discovered that depleting dopamine from the brains of rabbits by using reserpine caused them to become slow and rigid, similar to the symptoms of PD. He also found that injecting the rabbits with L-Dopa reversed these symptoms. This eventually led to the acceptance of levodopa as a medication for treating PD [68]. Levodopa is a dopamine precursor that unlike dopamine crosses the blood–brain barrier and is enzymatically converted into dopamine within the brain. This dopamine replacement offers significant symptomatic relief compared to untreated patients with PD. Cotzias was the first to use levodopa successfully in clinical practice. He countered the severe nausea experienced when using levodopa by starting with very small doses and gradually building up the dose. However, even in his initial series of patients dyskinesia was reported to be present and dose failures and motor fluctuations were also reported [69]. The addition of a dopa-decarboxylase inhibitor allowed considerably lower doses of levodopa to be used for the same clinical effect, allowing for reduced peripheral conversion of levodopa to dopamine and thus reducing nausea and other side effects thus cementing the role of levodopa as the mainstay of PD therapy [70]. However, the short half-life of levodopa is associated with long-term side effects including motor fluctuations and dyskinesia. Stimulating the dopamine receptors with long-acting dopamine agonists could potentially alleviate these side effects [71].

The pharmacotherapeutic basis of treatment of the motor symptoms is correction of the underlying dopamine deficit. The gold standard remains levodopa, which has the highest efficacy [72]. The bioavailability of levodopa is increased by combining it with a dopa decarboxylase inhibitor and/or with a catechol-O-methyltransferase (COMT) inhibitor [73]. Dopamine agonists may be used as an alternative and have

a significantly longer half-life but lower efficacy. In early stages the antiviral amantadine may provide adequate symptomatic benefit. Monoamine oxidase type B (MAO-B) inhibitors extend the duration of dopamine in the synaptic cleft and may also be used in early PD as monotherapy. Anticholinergics have been used based on the idea that there is a relative excess of acetylcholine, but their propensity to cause cognitive side effects limits their use [74].

Levodopa

Dopamine does not adequately cross the blood–brain barrier; hence, direct replacement is not possible. However, the dopamine precursor levodopa can cross the blood–brain barrier where it is enzymatically converted into dopamine. A significant amount of levodopa is metabolized in the periphery to dopamine. Carbidopa reduces this peripheral conversion, improving levodopa delivery to the brain and reducing peripheral side effects of dopamine such as nausea and orthostatic hypotension. The half-life of levodopa is increased from approximately 50 to 90 min by this combination. Thus, levodopa is rarely prescribed by itself but is used in the form of a combination tablet of carbidopa/levodopa (CD/LD) or Sinemet [75].

CD/LD is available in dosages of 10/100, 25/100, and 25/250 mg tablets. The initial target dose of CD/LD is generally one 25/100 mg tablet three times per day. It is advisable to initiate CD/LD slowly, starting with one-half of a 25/100 mg tablet twice a day for 1 week and then increasing by one-half tablet daily until symptoms are well controlled.

A controlled-release formulation of CD/LD (Sinemet-CR) is available in doses of 25/100 and 50/200 mg. This formulation is generally started with 25/100 mg/day and increased to 25/100 mg three times per day or 50/200 mg twice a day. Controlled-release preparations are not as well absorbed, and the bioavailability is 20–30 % lower than standard preparations [76]. CD/LD is also available in an orally disintegrating tablet (Parcopa). This formulation is available in the same strengths as immediate-release CD/LD and has similar bioavailability, safety, and efficacy. It is particularly useful in patients with swallowing difficulties [77].

Common acute adverse effects with CD/LD include nausea, vomiting, drowsiness, and orthostatic hypotension. Other side effects include diaphoresis, cardiac arrhythmias, and pedal edema. Cognitive side effects include confusion, vivid dreams, and hallucinations. The long-term use of CD/LD is associated with the development of dyskinesia and motor fluctuations, which are discussed below [78].

Dopamine Agonists

Pramipexole (Mirapex) and ropinirole (Requip) are the nonergot dopamine agonists in current use as oral agents. Older ergot derivatives such as bromocriptine and pergolide have long-term side effects such as cardiac valve damage and

retroperitoneal fibrosis and have fallen out of use. Apomorphine (Apokyn) is a post-synaptic nonergot dopamine agonist available as an injectable preparation mainly used as rescue therapy during "off" episodes. Rotigotine (Neupro) is a nonergot dopamine agonist formulated as a transdermal patch.

Unlike the direct replacement of dopamine by levodopa, dopamine agonists work by stimulation of the post-synaptic dopamine receptors. The oral agents have a significantly longer half-life than levodopa of around 6–8 h. This more continuous stimulation of the dopaminergic receptors may play a role in reducing the incidence of dyskinesia and motor fluctuations compared to levodopa [79]. However, while improvement in motor symptoms is based on their effect on D2 receptors in the basal ganglia, there is a relatively high affinity for D3 receptors as well, increasing the tendency to cause cognitive side effects such as excessive daytime somnolence (EDS), hallucinations, and compulsive behavior including gambling [80].

Pramipexole (Mirapex) is approved for use as monotherapy and adjunctive therapy in PD. Pramipexole acts on the D2, D3, and D4 dopamine receptors and has a half-life of 8–12 h. It reaches peak drug plasma concentration in approximately 2 h. It is excreted mostly unchanged in the urine. Pramipexole is initiated at 0.125 mg three times per day and increased over several weeks to a maximum dose of 1.5 mg three times per day [81]. An extended-release form of pramipexole (Mirapex ER) is also available that allows once-daily dosing [82].

Ropinirole (Requip) is approved for both monotherapy and adjunctive therapy in PD. It has affinity for the D2 dopamine receptors and no effect on the D1 or D5 dopaminergic receptors. The plasma half-life of ropinirole is approximately 6 h, with peak drug plasma concentrations occurring in 1–2 h. Ropinirole is initiated at 0.25 mg three times per day and increased over several weeks to a maximum dose of 8 mg three times per day [83]. An extended-release formulation, ropinirole (Requip XL), is also available, allowing once-daily dosing [84].

Rotigotine (Neupro) is a dopamine agonist that is available as a transdermal preparation and is approved both as monotherapy and as an adjunct to levodopa. Rotigotine for monotherapy is initiated at 2 mg/24 h and titrated weekly up to 6 mg/24 h [85]. When used as an adjunct to levodopa in patients with motor fluctuations, rotigotine may be started at 4 mg/24 h and titrated weekly up to 8 mg/24 h [86]. Rotigotine is generally well tolerated, with the most common adverse events being application-site reactions, gastrointestinal disturbances, somnolence, and headache. Application-site reactions are generally mild to moderate in severity. However, up to 3 % of patients had severe skin reactions [87].

Apomorphine (Apokyn) is approved for advanced PD as a rescue therapy for severe off periods and is available as a subcutaneous injection. It is a fast-acting, injectable dopamine agonist. It is rapidly absorbed in 10–60 min. However, the half-life of approximately 40 min results in an effect that lasts for only up to 90 min. It can be given every 2 h up to five times per day. A test dose of 2 mg (0.2 mL) is given in the physician's office, and the dose is titrated by 0.1-mL increments up to a maximum single dose of 0.6 mL [88]. Premedication with an anti-nausea medication, usually trimethobenzamide (Tigan), is required because apomorphine can cause severe nausea.

MAO Inhibitors

Metabolism of dopamine within dopaminergic terminals by MAO-B shortens the effect of dopamine. In addition, this metabolic pathway creates oxygen radicals including O_2^- and H_2O_2 that may potentially accelerate the death of dopaminergic neurons. MAO-B inhibitors are a treatment option for PD.

Selegiline (Eldepryl) is approved as an adjunct treatment to levodopa; however, it may also be used as monotherapy in early disease. The typical dose is 5 mg with breakfast and lunch. An orally disintegrating form of selegiline (Zelapar) is available in the strength of 1.25 mg. It is approved for use in advanced PD with motor fluctuations. The initial dose is 1.25 mg a day, which can be increased to 2.5 mg per day if clinically indicated. By the avoidance of first-pass metabolism, it results in higher concentrations of selegiline and lower concentrations of its metabolites compared with the 5-mg swallowed selegiline tablet [89].

Selegiline is generally well tolerated. The most common adverse effects include nausea, dizziness, insomnia, confusion, hallucinations, dry mouth, and orthostatic hypotension. It can lead to increased dyskinesia when used as an adjunct to levodopa therapy. As the dose of selegiline is increased, its selectivity to inhibit MAO-B is decreased, and inhibition of MAO-A can also occur; thus, it is important to not to increase the dose beyond 5 mg twice a day [90].

Rasagiline is an irreversible MAO-B inhibitor. It reaches peak plasma concentrations in approximately 1 h and has a half-life of approximately 3 h. However, since it irreversibly inhibits MAO-B, its therapeutic benefit is independent of its half-life. It is approved as monotherapy [91] in early disease at a dose of 1 mg/day, and in PD patients with motor fluctuations on levodopa starting at 0.5 mg/day, which can be increased to 1 mg/day [92].

Commonly observed adverse events with rasagiline monotherapy are arthralgia, depression, and gastrointestinal side effects. As an adjunct to levodopa, the common adverse effects included worsening of dyskinesia, weight loss, postural hypotension, arthralgia, gastrointestinal side effects, somnolence, and paresthesia. Unlike selegiline, rasagiline does not have amphetamine metabolites [93].

COMT Inhibitors

COMT inhibitors inhibit the action of catechol-O-methyl transferase, one of the metabolic pathways for the metabolism of levodopa. Tolcapone and entacapone are two COMT inhibitors used in the treatment of PD. The COMT inhibitor entacapone when given with CD/LD increases the area under the curve of levodopa by about 35 % and prolongs the half-life of levodopa to about 2.4 h while leaving the average peak levodopa plasma concentration unaffected, thus reducing the risk of peak-dose side effects [94].

Entacapone (Comtan) is approved for the management of motor fluctuations in PD. Its half-life is 0.4–0.7 h. It reduces the peripheral metabolism of levodopa, thereby increasing the half-life of levodopa to about 2.4 h. It is initiated at 200 mg with each dose of levodopa for a maximum of eight doses per day [95]. The common side effects of COMT-inhibitors are mostly related to increased dopaminergic stimulation. Dyskinesia, nausea, vomiting, and hallucinations are the most commonly seen dopaminergic adverse effects. These may be reduced by decreasing the levodopa dose. There is no known hepatotoxicity associated with entacapone and liver enzyme monitoring is not required. Diarrhea as an adverse effect usually begins at 6–12 weeks but can appear as early as 2 weeks after entacapone is started. If the diarrhea is bothersome, therapy must be discontinued. Urine discoloration is a harmless side effect that occurs in less than 10 % of patients [96].

The triple combination of carbidopa/levodopa/entacapone (Stalevo) is available in six different combinations: Stalevo 50 (carbidopa 12.5 mg/levodopa 50 mg/entacapone 200 mg), Stalevo 75 (carbidopa 18.75 mg/levodopa 75 mg/entacapone 200 mg), Stalevo 100 (carbidopa 25 mg/levodopa 100 mg/entacapone 200 mg), Stalevo 125 (carbidopa 31.25 mg/levodopa 125 mg/entacapone 200 mg), Stalevo 150 (carbidopa 37.5 mg/levodopa 150 mg/entacapone 200 mg), and Stalevo 200 (carbidopa 50 mg/levodopa 200 mg/entacapone 200 mg). This triple combination is indicated in PD patients as a substitute for immediate-release carbidopa/levodopa and entacapone previously administered separately [97].

Tolcapone (Tasmar) has a half-life of approximately 2–3 h with maximum plasma concentrations occurring in approximately 2 h. It is initiated at 100 mg three times a day and increased to 200 mg three times a day if needed [98]. Tolcapone should always be used with levodopa. Due to the risk of fatal hepatotoxicity, it may only be used in PD patients who have tried all other antiparkinsonian medications, and serum ALT and AST should be tested at baseline, every 2–4 weeks for the first 6 months, and then as clinically indicated. Tolcapone should be discontinued if the patient does not have a response or in the event of a two times increase in the upper limit of ALT and AST [99].

Anticholinergics and Amantadine

Anticholinergics were used in the treatment of PD before the discovery of levodopa. The basis for using these drugs is that in PD the nigral dopaminergic neurons that inhibit the GABAergic output from the striatum are lost. This allows cholinergic neurons in the striatum to exert an unopposed excitatory effect on these GABAergic neurons with resulting inhibition of the motor system. Anticholinergic drugs can reduce this effect. However, they are poorly tolerated by elderly patients due to their cognitive side effects. Other antimuscarinic side effects such as dry mouth, constipation, and reduced bladder outflow may also occur. Their use is mostly restricted to patients with tremor that is intractable to levodopa treatment [100].

Anticholinergics are generally well absorbed orally and usually require dosing two or three times a day. Anticholinergics most commonly used in the treatment of PD include trihexyphenidyl (Artane) and benztropine (Cogentin). Anticholinergics should be started at low doses and increased very slowly. Contraindications include narrow-angle glaucoma, tachycardia, prostate hypertrophy, gastrointestinal obstruction, and megacolon. Common side effects include blurring of vision, nausea, constipation, urinary retention, and dry mouth. Confusion, hallucinations, psychosis, and sedation may also occur. Central side effects occur more often in the elderly and in patients with impaired cognitive function [101].

Amantadine is a glutamate antagonist that increases release of dopamine at the nerve terminals and has anticholinergic properties. It may be used in early PD, but cognitive side effects may occur due to its anticholinergic properties. Due to its glutamate antagonist properties, it has a role as an anti-dyskinetic agent in later stages of PD [102]. Amantadine is well absorbed orally, with peak blood levels occurring in 2–4 h. It should be avoided in patients with renal failure. The usual dose is 200–300 mg/day in divided doses. Side effects of amantadine include dizziness, anxiety, impaired coordination, insomnia, and nervousness. Nausea and vomiting occur in 5–10 % of patients. In some patients, pedal edema and a type of skin rash called livedo reticularis can require discontinuation of therapy [103].

Management of Motor Fluctuations and Dyskinesia

While the immediate response to levodopa is often dramatic, the long-term use is limited by the development of motor fluctuations. The most common of these are an end-of-dose wearing off with a return of symptoms before the next dose is due, also called the wearing-off effect. The duration of response becomes increasingly shorter and patients who were previously well controlled on three to four doses a day may need a higher frequency of dosing. Some 40–50 % of patients on levodopa monotherapy will experience a degree of motor fluctuations at the 5-year mark [104]. Over time the fluctuations may occur at random with respect to the timing of medications described as the on–off effect. Dose-failures may occur, and the latency to clinical effect may be prolonged [105]. The addition of a COMT inhibitor or a MAO-B inhibitor can increase the duration of action of levodopa, thus allowing for a smoother therapeutic effect. Adding a dopamine agonist as an adjunct therapy may also reduce wearing off, as these drugs have a longer half-life than levodopa [106].

Dyskinesia is another limiting factor in the long-term use of levodopa. These occur in the form of involuntary choreiform movements, usually at the peak of the levodopa dose. However, other forms, including end-of-dose dyskinesia and diphasic dyskinesia, are also seen [107]. The incidence of dyskinesia in patients on CD/LD monotherapy was approximately 40 % at the 5-year mark compared with an incidence of approximately 10 % on ropinirole or pramipexole. Most dyskinesias represent a peak-dose response to levodopa, thus reducing individual doses, and

administering doses more frequently can help reduce dyskinesia. In patients who have dyskinesia, switching from sustained-release formulations of levodopa to regular formulations may reduce the duration of the dyskinesia after any given dose. Amantadine also has a role as an anti-dyskinetic agent [108].

Management of Cognitive and Psychiatric Symptoms

Anxiety and depression are common comorbid symptoms of PD and may even precede the onset of motor symptoms. A wide variety of selective serotonin uptake inhibitors (SSRIs) have been successfully used in the treatment of PD. These drugs must be used with caution when patients are on MAO-B inhibitors. Benzodiazepines may be used in the treatment of anxiety, but long-term use should be avoided if possible [109].

Dementia is a common finding in later stages of PD. Rivastigmine showed a beneficial effect in PD-associated dementia both as an oral preparation and as a transdermal patch. GI side effects are less common with the patch, but skin irritation may be a limiting factor in some cases [110]. PD is also associated with hallucinations, paranoid symptoms, and psychosis in later stages. The dopamine agonists are more likely to have these side effects because they have a relatively high affinity for D3 dopamine receptors present in the limbic system. Traditional neuroleptics such as haloperidol should be avoided because they can cause a marked worsening of motor symptoms of PD due to their dopamine antagonist effects. Of the novel neuroleptics, clozapine and quetiapine have been used with some degree of success, but clozapine requires frequent monitoring for agranulocytosis [111].

Treatment of Nonmotor Symptoms

While PD has been recognized as a movement disorder, its nonmotor symptoms have been generally less well recognized though documented in the literature. James Parkinson himself described sleep disorders, constipation, urinary incontinence, and delirium in his seminal essay. Nonmotor symptoms can occur at any stage of the disease including early PD and can even be a marker of the disease state prior to development of motor symptoms, the so-called premotor phase of the disease [112].

In addition to the cognitive and psychiatric symptoms discussed above, hyposmia, disturbances of sleep–wake cycle regulation, and features of autonomic dysfunction, including orthostatic hypotension, urogenital dysfunction, and constipation, are commonly seen [113]. There is no specific treatment for hyposmia. Sleep–wake cycle disorders in PD include insomnia, EDS, and REM sleep behavior disorder (RBD) [114]. Modafinil was shown to be helpful in treating EDS in a small clinical trial [115]. Attention to good sleep hygiene is important in

addressing insomnia. Quetiapine can be helpful in insomnia in the setting of PD; however, long-term use should be approached with caution [116]. Treatment options for RBD include benzodiazepines and melatonin. Clonazepam is the preferred benzodiazepine as it is long-acting and lasts through the night. It can also help reduce off-state dystonia that may occur through the night as the dopaminergic medications wear off. The mechanism of action of clonazepam may include controlling phasic locomotor activity at the brainstem level and modifying dream content in REM sleep [117].

Orthostatic hypotension when occurring soon after diagnosis raises suspicion of a parkinson-plus syndrome such as MSA. However, it is common and can have a significant adverse impact on the quality of life in the later stages of PD [118]. Management includes non-pharmacological measures such as increasing salt in the diet and pressure stockings. Fludrocortisone can also be helpful in this setting [119]. Midodrine has been shown to be helpful in neurogenic orthostatic hypotension and can also be helpful in the PD setting [120]. Botulinum toxin for sialorrhea, sildenafil for erectile dysfunction, and lubiprostone and probiotics for constipation are other suggestions for the management of these troubling non-motor symptoms. There is a great need for well-designed clinical trials to allow firm evidence-based recommendations for non-motor PD symptoms [121].

Neuroprotective Strategies

There is no drug with a proven neuroprotective effect in PD. Neuroprotective strategies are generally aimed at reducing oxidative stress or improving handling of free radicals through the use of antioxidant molecules. The DATATOP trial, one of the earliest studies of neuroprotection, compared selegiline with high-dose vitamin E in PD. The endpoint was the delay in the need for symptomatic treatment with levodopa. While vitamin E was no better than placebo, patients on selegiline required levodopa about 6 months later. Subsequent studies, however, indicated that this was due to a mild symptomatic benefit of selegiline rather than a true neuroprotective effect [72]. The ADAGIO trial used a delayed start design with placebo compared to patients started on rasagiline immediately or 9 months after the baseline visit. All groups were followed for a total of 18 months from the baseline visit. While the 1 mg dose of rasagiline met the hierarchical statistical criteria, the 2 mg dose failed to do so. Possible explanations for failure of the 2-mg doses that were proposed include a U-shaped dose–response effect and the presence of a "floor effect" on the rating scale used in the study, with patients with the mildest disease failing to show benefit. A post-hoc analysis did reveal a statistically significant difference in the most severely affected quartile even on the 2-mg dose [122]. Coenzyme Q10 was hypothesized to have a neuroprotective effect due to its role as an antioxidant and free radical scavenger. However, clinical trials have failed to support any neuroprotective role for Coenzyme Q10 in PD [123].

Surgical Treatment of Parkinson's Disease

With the advent of levodopa, the surgical treatment of PD receded into the background for some years. However, with time the limitations of levodopa treatment in the long-term, including motor fluctuations and dyskinesia, led to the recognition that surgical treatment could play a role in selected cases. Thalamotomy helped control intractable tremor, and pallidotomy helped reduce severe dyskinesia. The discovery that high-frequency stimulation of the surgical targets could control symptoms while offering a relative degree of reversibility in case of suboptimal target localization led to a resurgence of surgical treatment for PD. Deep brain stimulation (DBS) has become part of standard of care in selected patients in the later stages of PD [124].

The initial targets for DBS surgery were based on the experience of lesioning techniques of thalamotomy and pallidotomy. The corresponding targets included the ViM nucleus of the thalamus and the internal segment of the globus pallidus (GPi). The ViM was found to be an excellent target for control of tremor from PD; however, its impact on other features was limited. The GPi was found to be a good target in patients with troublesome dyskinesias [124]. The subthalamic nucleus (STN) was also explored as a surgical target and was found to be of benefit in control of overall symptoms of PD as well as allowing for a reduction in medication dosing to a somewhat greater extent than with GPi DBS. The current consensus appears to be that both GPi and STN are viable targets for overall control of PD symptoms including tremor. The choice of target is usually determined by institutional preferences. Alterative targets have included the pedunculopontine nucleus for patients with prominent freezing of gait. However, clinical experience is limited for alternative targets [125].

Appropriate patient selection is critical with respect to both the type of parkinsonism and duration and severity of the disease. Only patients with idiopathic PD are suitable candidates and those with parkinson-plus syndromes should be excluded. Appendicular symptoms such as tremor and dyskinesia improve more than axial symptoms such as gait and balance. In general, it is difficult to improve symptoms beyond the level seen in the patient's best "on-state" prior to surgery. There is approximately a 2 % risk of hemorrhage that can lead to greater disability or even death. Hence, surgery should only be offered to patients who have either significant motor fluctuations or specific symptoms such as tremor or dyskinesia that are intractable to medication adjustments. On the other hand, surgery should not be offered too late in the course of the disease when both physical debilitation and cognitive symptoms can play a limiting role preventing a successful outcome [125]. Alternative surgical therapies such as stem cell implantation, nerve growth factor infusion, and gene therapy are not part of current clinical practice, although research is ongoing both at the basic science level and in the form of early clinical trials [126].

References

1. Dalvi A. Parkinsonism. In: Bope E, Kellerman R, editors. Conn's current therapy. Philadelphia: Saunders Elsevier; 2013.
2. Dalvi A. Parkinsonism. Dis Mon. 2012;58:690–707.
3. Bhidayasiri R, Reichmann H. Different diagnostic criteria for Parkinson disease: what are the pitfalls? J Neural Transm. 2013;120:619–25.
4. Khan TS. Off spells and dyskinesias: pharmacologic management of motor complications. Cleve Clin J Med. 2012;79 Suppl 2:S8–13.
5. Pandya M, Kubu CS, Giroux ML. Parkinson disease: not just a movement disorder. Cleve Clin J Med. 2008;75:856–64.
6. Watson GS, Leverenz JB. Profile of cognitive impairment in Parkinson's disease. Brain Pathol. 2010;20:640–5.
7. Cummings JL, Henchcliffe C, Schaier S, Simuni T, Waxman A, Kemp P. The role of dopaminergic imaging in patients with symptoms of dopaminergic system neurodegeneration. Brain. 2011;134:3146–66.
8. Parkinson J. An essay on the shaking palsy. London: Sherwood, Neeley and Jones; 1817.
9. Gower W. A manual of diseases of the nervous system. Philadelphia: P. Blakiston; 1888.
10. Tanner CM, Ottman R, Goldman SM, Ellenberg J, Chan P, Mayeux R, et al. Parkinson disease in twins: an etiologic study. JAMA. 1999;281:341–6.
11. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997;276:2045–7.
12. Moore DJ, West AB, Dawson VL, Dawson TM. Molecular pathophysiology of Parkinson's disease. Annu Rev Neurosci. 2005;28:57–87.
13. Burke WJ, Kumar VB, Pandey N, Panneton WM, Gan Q, Franko MW, et al. Aggregation of alpha-synuclein by DOPAL, the monoamine oxidase metabolite of dopamine. Acta Neuropathol. 2008;115:193–203.
14. Xu J, Kao SY, Lee FJ, Song W, Jin LW, Yankner BA. Dopamine-dependent neurotoxicity of alpha-synuclein: a mechanism for selective neurodegeneration in Parkinson disease. Nat Med. 2002;8:600–6.
15. Orr CF, Rowe DB, Halliday GM. An inflammatory review of Parkinson's disease. Prog Neurobiol. 2002;68:325–40.
16. Hubble JP, Cao T, Hassanein RE, Neuberger JS, Koller WC. Risk factors for Parkinson's disease. Neurology. 1993;43:1693–7.
17. Wang WZ, Fang XH, Cheng XM, Jiang DH, Lin ZJ. A case-control study on the environmental risk factors of Parkinson's disease in Tianjin, China. Neuroepidemiology. 1993;12:209–18.
18. Wright Willis A, Evanoff BA, Lian M, Criswell SR, Racette BA. Geographic and ethnic variation in Parkinson disease: a population-based study of US Medicare beneficiaries. Neuroepidemiology. 2010;34:143–51.
19. Lock EA, Zhang J, Checkoway H. Solvents and Parkinson disease: a systematic review of toxicological and epidemiological evidence. Toxicol Appl Pharmacol. 2013;266:345–55.
20. Goldman SM, Quinlan PJ, Ross GW, Marras C, Meng C, Bhudhikanok GS, et al. Solvent exposures and Parkinson disease risk in twins. Ann Neurol. 2012;71:776–84.
21. Racette BA, Criswell SR, Lundin JI, Hobson A, Seixas N, Kotzbauer PT, et al. Increased risk of parkinsonism associated with welding exposure. Neurotoxicology. 2012;33:1356–61.
22. Mortimer JA, Borenstein AR, Nelson LM. Associations of welding and manganese exposure with Parkinson disease: review and meta-analysis. Neurology. 2012;79:1174–80.
23. Tan EK, Skipper LM. Pathogenic mutations in Parkinson disease. Hum Mutat. 2007;28:641–53.
24. Tanner CM. Is the cause of Parkinson's disease environmental or hereditary? Evidence from twin studies. Adv Neurol. 2003;91:133–42.

25. Wood-Kaczmar A, Gandhi S, Wood NW. Understanding the molecular causes of Parkinson's disease. Trends Mol Med. 2006;12:521–8.
26. Gosal D, Ross OA, Toft M. Parkinson's disease: the genetics of a heterogeneous disorder. Eur J Neurol. 2006;13:616–27.
27. Spratt DE, Martinez-Torres RJ, Noh YJ, Mercier P, Manczyk N, Barber KR, et al. A molecular explanation for the recessive nature of parkin-linked Parkinson's disease. Nat Commun. 2013;4:1983.
28. Rango M, Arighi A, Marotta G, Ronchi D, Bresolin N. PINK1 parkinsonism and Parkinson disease: distinguishable brain mitochondrial function and metabolomics. Mitochondrion. 2013;13:59–61.
29. Johnson BN, Charan RA, LaVoie MJ. Recognizing the cooperative and independent mitochondrial functions of Parkin and PINK1. Cell Cycle. 2012;11:2775–6.
30. Abou-Sleiman PM, Healy DG, Wood NW. Causes of Parkinson's disease: genetics of DJ-1. Cell Tissue Res. 2004;318:185–8.
31. Miyazaki S, Yanagida T, Nunome K, Ishikawa S, Inden M, Kitamura Y, et al. DJ-1-binding compounds prevent oxidative stress-induced cell death and movement defect in Parkinson's disease model rats. J Neurochem. 2008;105:2418–34.
32. Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S, et al. International LRRK2 consortium. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol. 2008;7:583–90.
33. Ozelius LJ, Senthil G, Saunders-Pullman R, Ohmann E, Deligtisch A, Tagliati M, et al. LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. N Engl J Med. 2006;354:424–5.
34. Lesage S, Dürr A, Tazir M, Lohmann E, Leutenegger AL, Janin S, et al. French Parkinson's Disease Genetics Study Group. LRRK2 G2019S as a cause of Parkinson's disease in North African Arabs. N Engl J Med. 2006;354:422–3.
35. Puschmann A. Monogenic Parkinson's disease and parkinsonism: clinical phenotypes and frequencies of known mutations. Parkinsonism Relat Disord. 2013;19:407–15.
36. West AB, Moore DJ, Biskup S, Bugayenko A, Smith WW, Ross CA, et al. Parkinson's disease-associated mutations in leucine-rich repeat kinase 2 augment kinase activity. Proc Natl Acad Sci U S A. 2005;102:16842–7.
37. Gómez-Suaga P, Fdez E, Blanca Ramírez M, Hilfiker S. A link between autophagy and the pathophysiology of LRRK2 in Parkinson's disease. Parkinsons Dis. 2012;2012:324521.
38. Zhang ZJ, Burgunder JM, An XK, Wu Y, Chen WJ, Zhang JH, et al. Lack of evidence for association of a UCH-L1 S18Y polymorphism with Parkinson's disease in a Han-Chinese population. Neurosci Lett. 2008;442:200–2.
39. Liu Y, Fallon L, Lashuel HA, Liu Z, Lansbury Jr PT. The UCH-L1 gene encodes two opposing enzymatic activities that affect alpha-synuclein degradation and Parkinson's disease susceptibility. Cell. 2002;111:209–18.
40. Ardley HC, Scott GB, Rose SA, Tan NG, Robinson PA. UCH-L1 aggresome formation in response to proteasome impairment indicates a role in inclusion formation in Parkinson's disease. J Neurochem. 2004;90:379–91.
41. Kim RH, Smith PD, Aleyasin H, Hayley S, Mount MP, Pownall S, et al. Hypersensitivity of DJ-1-deficient mice to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and oxidative stress. Proc Natl Acad Sci U S A. 2005;102:5215–20.
42. Irrcher I, Aleyasin H, Seifert EL, Hewitt SJ, Chhabra S, Phillips M, et al. Loss of the Parkinson's disease-linked gene DJ-1 perturbs mitochondrial dynamics. Hum Mol Genet. 2010;19:3734–46.
43. Ransmayr G. Constantin von Economo's contribution to the understanding of movement disorders. Mov Disord. 2007;22:469–75.
44. Dale RC, Webster R, Gill D. Contemporary encephalitis lethargica presenting with agitated catatonia, stereotypy, and dystonia-parkinsonism. Mov Disord. 2007;22:2281–4.
45. Woulfe J, Hoogendoorn H, Tarnopolsky M, Muñoz DG. Monoclonal antibodies against Epstein–Barr virus cross-react with alpha-synuclein in human brain. Neurology. 2000;55:1398–401.

46. McGeer PL, Yasojima K, McGeer EG. Inflammation in Parkinson's disease. Adv Neurol. 2001;86:83–9.
47. Kumar A, Calne SM, Schulzer M, Mak E, Wszolek Z, Van Netten C, et al. Clustering of Parkinson disease: shared cause or coincidence? Arch Neurol. 2004;61:1057–60.
48. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. Nature. 1997;388:839–40.
49. Marques O, Outeiro TF. Alpha-synuclein: from secretion to dysfunction and death. Cell Death Dis. 2012;3:e350.
50. Goedert M, Spillantini MG, Del Tredici K, Braak H. 100 years of Lewy pathology. Nat Rev Neurol. 2013;9:13–24.
51. Dunning CJ, Reyes JF, Steiner JA, Brundin P. Can Parkinson's disease pathology be propagated from one neuron to another? Prog Neurobiol. 2012;97:205–19.
52. George S, Rey NL, Reichenbach N, Steiner JA, Brundin P. α-Synuclein: the long distance runner. Brain Pathol. 2013;23:350–7.
53. Kordower JH, Brundin P. Lewy body pathology in long-term fetal nigral transplants: is Parkinson's disease transmitted from one neural system to another? Neuropsychopharmacology. 2009;34:254.
54. McGeer PL, McGeer EG. Glial reactions in Parkinson's disease. Mov Disord. 2008;23: 474–83.
55. Schwab C, McGeer PL. Inflammatory aspects of Alzheimer disease and other neurodegenerative disorders. J Alzheimers Dis. 2008;13:359–69.
56. Pabon MM, Jernberg JN, Morganti J, Contreras J, Hudson CE, Klein RL, et al. A spirulina-enhanced diet provides neuroprotection in an α-synuclein model of Parkinson's disease. PLoS One. 2012;7:e45256.
57. Garrido-Gil P, Joglar B, Rodriguez-Perez AI, Guerra MJ, Labandeira-Garcia JL. Involvement of PPAR-γ in the neuroprotective and anti-inflammatory effects of angiotensin type 1 receptor inhibition: effects of the receptor antagonist telmisartan and receptor deletion in a mouse MPTP model of Parkinson's disease. J Neuroinflammation. 2012;9:38.
58. Ridder DA, Schwaninger M. In search of the neuroprotective mechanism of thiazolidinediones in Parkinson's disease. Exp Neurol. 2012;238:133–7.
59. Ulusoy GK, Celik T, Kayir H, Gürsoy M, Isik AT, Uzbay TI. Effects of pioglitazone and retinoic acid in a rotenone model of Parkinson's disease. Brain Res Bull. 2011;85:380–4.
60. Chan CS, Gertler TS, Surmeier DJ. A molecular basis for the increased vulnerability of substantia nigra dopamine neurons in aging and Parkinson's disease. Mov Disord. 2010;25 Suppl 1:S63–70.
61. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science. 1983;219:979–80.
62. McCormack AL, Thiruchelvam M, Manning-Bog AB, Thiffault C, Langston JW, Cory-Slechta DA, et al. Environmental risk factors and Parkinson's disease: selective degeneration of nigral dopaminergic neurons caused by the herbicide paraquat. Neurobiol Dis. 2002;10: 119–27.
63. Jenner P. Oxidative stress and Parkinson's disease. Handb Clin Neurol. 2007;83:507–20.
64. Jenner P, Olanow CW. The pathogenesis of cell death in Parkinson's disease. Neurology. 2006;66:S24–36.
65. Cipriani S, Chen X, Schwarzschild MA. Urate: a novel biomarker of Parkinson's disease risk, diagnosis and prognosis. Biomark Med. 2010;4:701–12.
66. Schapira AH. Evidence for mitochondrial dysfunction in Parkinson's disease—a critical appraisal. Mov Disord. 1994;9:125–38.
67. McInnes J. Insights on altered mitochondrial function and dynamics in the pathogenesis of neurodegeneration. Transl Neurodegener. 2013;2:12.
68. Carlsson A. Thirty years of dopamine research. Adv Neurol. 1993;60:1–10.
69. Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. N Engl J Med. 1967;276:374–9.

70. Rao SK, Vakil SD, Calne DB, Hilson A. Augmenting the action of levodopa. Postgrad Med J. 1972;48:653–6.
71. Tambasco N, Simoni S, Marsili E, Sacchini E, Murasecco D, Cardaioli G, et al. Clinical aspects and management of levodopa-induced dyskinesia. Parkinsons Dis. 2012;2012:745947.
72. Rascol O, Lozano A, Stern M, Poewe W. Milestones in Parkinson's disease therapeutics. Mov Disord. 2011;26:1072–82.
73. Merello M, Lees AJ, Webster R, Bovingdon M, Gordin A. Effect of entacapone, a peripherally acting catechol-O-methyltransferase inhibitor, on the motor response to acute treatment with levodopa in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1994;57:186–9.
74. Schapira AH. Present and future drug treatment for Parkinson's disease. J Neurol Neurosurg Psychiatry. 2005;76:1472–8.
75. Markham C, Diamond SG, Treciokas LJ. Carbidopa in Parkinson disease and in nausea and vomiting of levodopa. Arch Neurol. 1974;31:128–33.
76. LeWitt PA, Nelson MV, Berchou RC, Galloway MP, Kesaree N, Kareti D, et al. Controlled-release carbidopa/levodopa (Sinemet 50/200 CR4): clinical and pharmacokinetic studies. Neurology. 1989;39:45–53. discussion 59.
77. Parcopa: a rapidly dissolving formulation of carbidopa/levodopa. Med Lett Drugs Ther. 2005;47(1201):12. PubMed PMID: 15706700.
78. Poewe W, Antonini A, Zijlmans JC, Burkhard PR, Vingerhoets F. Levodopa in the treatment of Parkinson's disease: an old drug still going strong. Clin Interv Aging. 2010;5:229–38.
79. Watts RL. The role of dopamine agonists in early Parkinson's disease. Neurology. 1997;49:S34–48.
80. Voon V, Mehta AR, Hallett M. Impulse control disorders in Parkinson's disease: recent advances. Curr Opin Neurol. 2011;24:324–30.
81. Shannon KM, Bennett Jr JP, Friedman JH. Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. The Pramipexole Study Group. Neurology. 1997;49:724–8.
82. Hametner EM, Seppi K, Poewe W. Role and clinical utility of pramipexole extended release in the treatment of early Parkinson's disease. Clin Interv Aging. 2012;7:83–8.
83. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med. 2000;342:1484–91.
84. Nashatizadeh MM, Lyons KE, Pahwa R. A review of ropinirole prolonged release in Parkinson's disease. Clin Interv Aging. 2009;4:179–86.
85. Watts RL, Jankovic J, Waters C, Rajput A, Boroojerdi B, Rao J. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. Neurology. 2007;68:272–6.
86. LeWitt PA, Lyons KE, Pahwa R, SP 650 Study Group. Advanced Parkinson disease treated with rotigotine transdermal system: PREFER Study. Neurology. 2007;68:1262–7.
87. Sanford M, Scott LJ. Rotigotine transdermal patch: a review of its use in the treatment of Parkinson's disease. CNS Drugs. 2011;2:699–719.
88. Stacy M, Silver D. Apomorphine for the acute treatment of "off" episodes in Parkinson's disease. Parkinsonism Relat Disord. 2008;14:85–92.
89. Elmer LW, Bertoni JM. The increasing role of monoamine oxidase type B inhibitors in Parkinson's disease therapy. Expert Opin Pharmacother. 2008;9:2759–72.
90. Olanow CW, Mytilineou C, Tatton W. Current status of selegiline as a neuroprotective agent in Parkinson's disease. Mov Disord. 1998;13 Suppl 1:55–8.
91. Stern MB, Marek KL, Friedman J, Hauser RA, LeWitt PA, Tarsy D, et al. Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson's disease patients. Mov Disord. 2004;19:916–23.
92. Stocchi F, Rabey JM. Effect of rasagiline as adjunct therapy to levodopa on severity of OFF in Parkinson's disease. Eur J Neurol. 2011;18:1373–8.
93. Perez-Lloret S, Rascol O. Safety of rasagiline for the treatment of Parkinson's disease. Expert Opin Drug Saf. 2011;10:633–43.

94. Marsala SZ, Gioulis M, Ceravolo R, Tinazzi M. A systematic review of catechol-O-methyltransferase inhibitors: efficacy and safety in clinical practice. Clin Neuropharmacol. 2012;35:185–90.
95. Rinne UK, Larsen JP, Siden A, Worm-Petersen J. Entacapone enhances the response to levodopa in Parkinsonian patients with motor fluctuations. Nomecomt Study Group. Neurology. 1998;51:1309–14.
96. Brooks DJ. Safety and tolerability of COMT inhibitors. Neurology. 2004;62:S39–46.
97. Hauser RA. Levodopa/carbidopa/entacapone (Stalevo). Neurology. 2004;62:S64–71.
98. Kurth MC, Adler CH, Hilaire MS, Singer C, Waters C, LeWitt P, et al. Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomized, placebo-controlled trial. Tolcapone Fluctuator Study Group I. Neurology. 1997;48:81–7.
99. Truong DD. Tolcapone: review of its pharmacology and use as adjunctive therapy in patients with Parkinson's disease. Clin Interv Aging. 2009;4:109–13.
100. Brocks DR. Anticholinergic drugs used in Parkinson's disease: an overlooked class of drugs from a pharmacokinetic perspective. J Pharm Pharm Sci. 1999;2:39–46.
101. Fahn S, Burke R, Stern Y. Antimuscarinic drugs in the treatment of movement disorders. Prog Brain Res. 1990;84:389–97.
102. Blanchet PJ, Metman LV, Chase TN. Renaissance of amantadine in the treatment of Parkinson's disease. Adv Neurol. 2003;91:251–7.
103. Crosby N, Deane KH, Clarke CE. Amantadine in Parkinson's disease. Cochrane Database Syst Rev. 2003;1:CD003468.
104. Stocchi F, Jenner P, Obeso JA. When do levodopa motor fluctuations first appear in Parkinson's disease? Eur Neurol. 2010;63:257–66.
105. Melamed E, Ziv I, Djaldetti R. Management of motor complications in advanced Parkinson's disease. Mov Disord. 2007;22:S379–84.
106. Pahwa R, Lyons KE. Levodopa-related wearing-off in Parkinson's disease: identification and management. Curr Med Res Opin. 2009;25:841–9.
107. Fahn S. The spectrum of levodopa-induced dyskinesias. Ann Neurol. 2000;47:S2–9.
108. Pahwa R, Lyons KE. Early diagnosis of Parkinson's disease: recommendations from diagnostic clinical guidelines. Am J Manag Care. 2010;16:S94–9.
109. Weintraub D, Burn DJ. Parkinson's disease: the quintessential neuropsychiatric disorder. Mov Disord. 2011;26:1022–31.
110. Svenningsson P, Westman E, Ballard C, Aarsland D. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. Lancet Neurol. 2012;11:697–707.
111. Starkstein SE, Brockman S, Hayhow BD. Psychiatric syndromes in Parkinson's disease. Curr Opin Psychiatry. 2012;25:468–72.
112. Dalvi A. Premotor symptoms. In: Pahwa R, Lyons KE, editors. Handbook of Parkinson's disease. New York: Informa; 2013.
113. Poewe W. Non-motor symptoms in Parkinson's disease. Eur J Neurol. 2008;15:S14–20.
114. Comella CL. Sleep disorders in Parkinson's disease: an overview. Mov Disord. 2007;22: S367–73.
115. Högl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K, et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. Sleep. 2002;25:905–9.
116. Juri C, Chaná P, Tapia J, Kunstmann C, Parrao T. Quetiapine for insomnia in Parkinson disease: results from an open-label trial. Clin Neuropharmacol. 2005;28:185–7.
117. Lapierre O, Montplaisir J. Polysomnographic features of REM sleep behavior disorder: development of a scoring method. Neurology. 1992;42:1371–4.
118. Sánchez-Ferro A, Benito-León J, Gómez-Esteban JC. The management of orthostatic hypotension in Parkinson's disease. Front Neurol. 2013;4:64.
119. Schoffer KL, Henderson RD, O'Maley K, O'Sullivan JD. Nonpharmacological treatment, fludrocortisone, and domperidone for orthostatic hypotension in Parkinson's disease. Mov Disord. 2007;22:1543–9.

120. Low PA, Gilden JL, Freeman R, Sheng KN, McElligott MA. Efficacy of midodrine vs placebo in neurogenic orthostatic hypotension. A randomized, double-blind multicenter study. Midodrine Study Group. JAMA. 1997;277:1046–51.
121. Perez-Lloret S, Rey MV, Pavy-Le Traon A, Rascol O. Emerging drugs for autonomic dysfunction in Parkinson's disease. Expert Opin Emerg Drugs. 2013;18:39–53.
122. Schapira AH. Monoamine oxidase B inhibitors for the treatment of Parkinson's disease: a review of symptomatic and potential disease-modifying effects. CNS Drugs. 2011;25: 1061–71.
123. Storch A, Jost WH, Vieregge P, Spiegel J, Greulich W, Durner J, et al. German Coenzyme Q(10) Study Group. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q(10) in Parkinson disease. Arch Neurol. 2007;64:938–44.
124. Rodriguez-Oroz MC, Moro E, Krack P. Long-term outcomes of surgical therapies for Parkinson's disease. Mov Disord. 2012;27:1718–28.
125. Bronstein JM, Tagliati M, Alterman RL, Lozano AM, Volkmann J, Stefani A, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. Arch Neurol. 2011;68:165.
126. Hickey P, Stacy M. Available and emerging treatments for Parkinson's disease: a review. Drug Des Devel Ther. 2011;5:241–54.