Parkinson's Disease

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Abstract Parkinson's Disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. The majority of cases are sporadic, commonly referred to as idiopathic Parkinson's disease (IPD). The cardinal clinical features are bradykinesia, rigidity, rest tremor, and postural instability. A flexed posture and the freezing phenomenon are also commonly seen.

Initial descriptions of Parkinson's disease (PD) and its management following the introduction of levodopa concentrated on the cardinal motor features. Long-term studies and clinicopathological correlation make it clear, however, that this is a disease with diverse effects, also affecting cognition, mood, autonomic function, and the sleep cycle. Patient care has accordingly become increasingly complex. With the exception of deep brain stimulation, diagnostic and therapeutic options have changed little in the past 20 years. Validated biomarkers and disease-modifying therapies are still required. This chapter aims to practically address common clinical issues and update the practitioner on advances in the field.

Keywords Parkinson's disease • Synucleinopathy • Lewy body • Neurodegeneration • Levodopa

Pathology

IPD arises as a result of degeneration of neurons in the substantia nigra pars compacta. The pathological hallmark is the α(alpha)-synuclein containing Lewy body, an eosinophilic, proteinaceous cytoplasmic inclusion seen in surviving neurons (Fig. 5.1).

Staining for Lewy pathology with antibodies to α(alpha)-synuclein indicates that the first location of pathologic change is in the olfactory apparatus and caudal brainstem, especially the dorsal motor nucleus of the vagus in the medulla. Neural involvement

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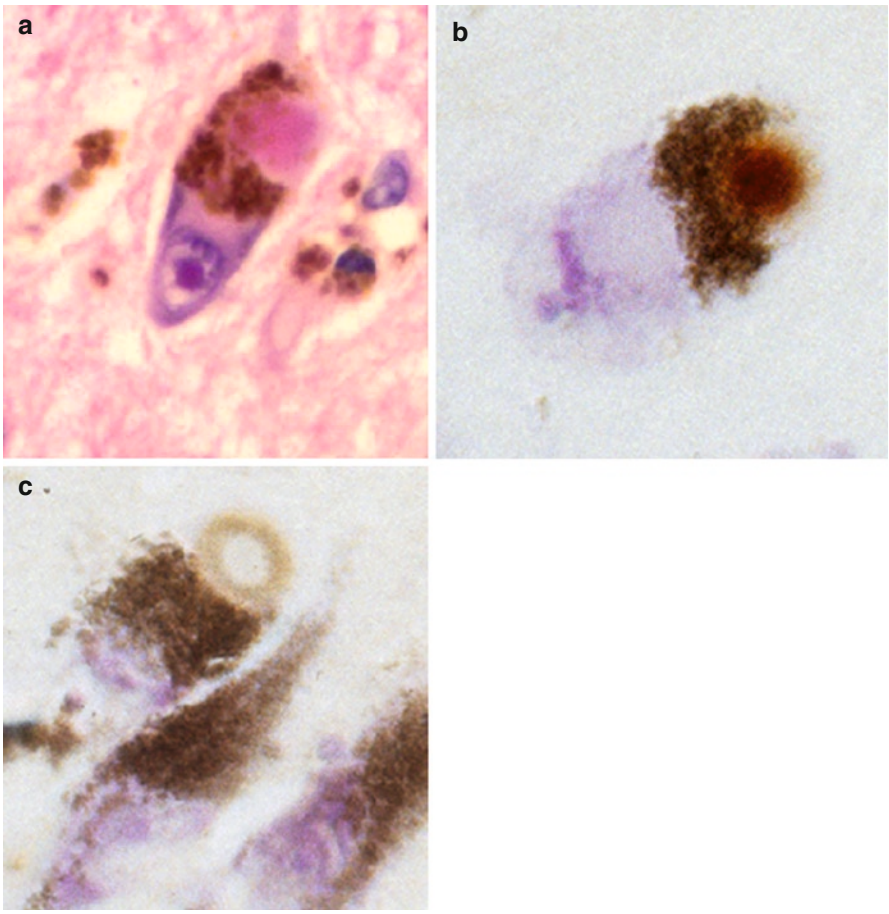


Fig. 5.1 (**a**) H and E staining of a substantia nigra neuron containing a Lewy body; (**b**) The core of each Lewy body stains more strongly for α(alpha)-synuclein than the characteristic halo (**c**), which is strongly immunoreactive for ubiquitin

progressively spreads rostrally up the brainstem in a fashion hypothesized by Braak and colleagues, who have studied the pattern of α(alpha)-synuclein involvement in autopsied brains. The cerebral cortex is involved late in this schema, in keeping with the evolution of cognitive impairment, (if not frank dementia) in patients with long-standing IPD. When the motor symptoms of IPD are evident, the substantia nigra already has lost about 60% of dopaminergic neurons, and the dopamine content in the striatum is about 80% less than normal. Involvement of non-dopaminergic neurons including cholinergic neurons in the nucleus basalis of Meynert, noradrenergic neurons in the locus coeruleus and serotonergic neurons in the midline raphe may be significant in the non-motor symptoms.

Diagnosis

The diagnosis of IPD remains essentially a clinical one. If made by a neurologist, the diagnosis based on clinical impression has been shown to have a positive predictive value of 76–98.6% for those working in a specialist movement disorders service. The United Kingdom Parkinson's Disease Society Brain Bank criteria are typically used in studies of IPD; bradykinesia with one of tremor, rigidity, and postural instability are required in the absence of exclusion criteria (Table 5.1). Retrospective application of these criteria to patients diagnosed with IPD in life demonstrates positive predictive values of between 82% and 92%. This diagnostic accuracy may be improved if a levodopa response and asymmetry are also sought but sensitivity may be lost.

Some physicians will use the "levodopa challenge" where a response to a single dose of up to 300 mg of levodopa is reassuring. Tremor-predominant forms of IPD may not, however, demonstrate any response to levodopa and some atypical forms of parkinsonism will, thus causing diagnostic confusion. Others avoid this challenge, particularly in younger patients, given concerns that even a single dose of levodopa may "prime" the basal ganglia for dyskinesia.

An important aspect of the initial and subsequent clinical assessments is to look for atypical features suggesting an alternative diagnosis, having important implications for predicting survival and treatment response. Some conditions mimicking IPD will require alternative treatment strategies (Table 5.2). Also, it is not uncommon for IPD to present with symptoms not readily attributed to the disease. Some of these patients will carry alternative diagnoses before the more obvious parkinsonian features appear (Table 5.3).

Table 5.1 Exclusion criteria for Parkinson's disease

- History of repeated strokes with stepwise progression
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crisis (unless drug induced)
- Neuroleptic exposure at time of diagnosis
- Sustained remission
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia
- Babinski sign
- Presence of cerebral tumor or communicating hydrocephalus on imaging
- Failure to respond to an adequate dose of levodopa (up to 2,000 mg)
- Scans without evidence of dopaminergic deficit (SWEDDs)

Table 5.2 Clinical features of the Parkinson-plus (Atypical) disorders

Progressive supranuclear palsy • Early falls • Prominent axial rigidity • Pure freezing of gait and early freezing • Arm abduction when walking • Frontalis overactivity • Vertical gaze palsy or "round the houses" vertical saccades • Deep naso-labial folds • Blepharospasm • Square-wave jerks • Slowing of horizontal saccades • Apraxia of eye opening • Characteristic voice is a hoarse, throaty growl, with some hesitation between words
Multiple systems atrophy • Prominent cerebellar or autonomic features • Flexed posture • Anterocollis • Myoclonus or polyminimyoclonus • Laryngeal stridor (may only be nocturnal) • Early orofacial dyskinesia with levodopa • Pyramidal tract signs (e.g., extensor plantar responses, spastic "catch" at wrist) • Purple discoloration of the feet due to abnormal vascular autonomics
Corticobasal degeneration • Unilateral dystonia • Alien-limb phenomenon • Unilateral stimulus sensitive myoclonus • Cortical sensory loss • Dyspraxia

Table 5.3 Parkinsonian symptoms and signs commonly attributed to other disorders

• Fatigue • Dyspnea • Bradyphrenia • Depression • Joint pain (particularly shoulder pain) • "Radicular" pain (true radicular pain may worsen in "off" states) • Foot cramps/dystonia • Dysphonia • Anxiety/panic attacks • "Weakness," affecting ability to rise from chairs or apparently unilateral weakness

Differential Diagnosis of Parkinsonism

Atypical Parkinsonism

Approximately three quarters of patients presenting with parkinsonism have typical motor features, and are most likely to have pathologically confirmed IPD. The remaining 25% of patients will have so-called atypical parkinsonism, also called Parkinson-plus syndromes. This group of primary degenerative parkinsonian disorders includes progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD) and are covered in Chap. 9. All may start with an asymmetrical clinical syndrome indistinguishable from IPD. These forms of parkinsonism all share a tendency to be poorly responsive to levodopa, be largely symmetrical (with the exception of corticobasal degeneration), and have little or no rest tremor (although myoclonus mimicking tremor may be evident). Table 5.2 highlights clinical features that should raise suspicion of an atypical parkinsonism.

Dementia with Lewy Bodies

Patients presenting with dementia before, or within 1 year of manifesting parkinsonism, are by convention given a diagnosis of dementia with Lewy bodies (DLB). Visual hallucinations are common and the course of cognitive impairment is typically fluctuating. Some patients will have prominent autonomic dysfunction. Patients with dementia beginning after 1 year are diagnosed with PD with dementia (PDD). Both these conditions may represent different points on the spectrum of "Lewy body disease" with a larger cortical burden of Lewy bodies than in patients with IPD.

Secondary Parkinsonism

Drug-Induced Parkinsonism

Parkinsonism can follow exposure to drugs with an antagonistic effect at D_2 receptors. This is the most common cause of secondary parkinsonism and is typically seen in patients requiring antipsychotic treatment. Newer, "atypical" neuroleptics with less affinity to the D_2 receptor are less likely to result in extrapyramidal side effects and are preferred when treating psychosis in IPD. The commonly used antiemetic drugs metoclopramide and prochlorperazine also have a D_2 antagonist effect. Other drugs known to induce parkinsonism include lithium, tetrabenazine, reserpine, valproate, and the calcium channel blockers, cinnarizine and flunarizine.

Drug withdrawal typically results in a slow improvement although latent parkinsonism may have been unmasked and full recovery may not occur.

Vascular Parkinsonism

This is also known as "lower body parkinsonism" due to prominent gait disturbance and relatively less arm involvement. Often, these patients will have early freezing, which is not typically seen in IPD. This is an important cause of parkinsonism in older patients and those with a history of vascular risk factors (particularly hypertension). The pathophysiology is related to small vessel disease with prominent periventricular ischemia. Patients with basal ganglia infarcts are more likely to respond to levodopa. Magnetic resonance imaging (MRI) of brain is useful to identify those patients who may have a vascular cause of parkinsonism. Other clinical features that can help differentiate vascular from idiopathic parkinsonism are a postural, more than, resting tremor and preserved olfaction.

Fragile X Pre-mutation

The pre-mutation state of Fragile X can present with tremor, parkinsonism, and autonomic features, and may therefore be misdiagnosed as either IPD or MSA. An accurate family history is vital, looking for evidence of a related child with learning disability or autism. The presence of ataxia is another important clue. In one series of 26 patients with pre-mutations of the FMR1 gene, 57% of cases had mild bradykinesia, resting tremor was present in 40%, and 71% had upper limb rigidity.

Others

Secondary parkinsonism can also occur following toxin exposure, including manganese, carbon disulphide, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

Rarely parkinsonism can arise as a consequence of central nervous system (CNS) tumors, more commonly supratentorial meningiomas causing basal ganglia compression than by direct tumor infiltration.

Functional parkinsonism is well recognized but rare. Clues to the diagnosis are a history of previous psychogenic illness, an abrupt onset, entrainment of tremor, selective disability, and distractibility.

Disorders That Can Mimic Parkinsonism

Essential Tremor

Essential tremor (ET) is one of the most common disorders mistaken for IPD, characterized by a postural and kinetic tremor without rest tremor. Patients with ET can have cogwheeling but without rigidity. Where there is a combination of a resting hand tremor with essential tremor, the physician should consider rest tremor appearing late in ET, or the combined resting-postural tremor syndrome.

Parkinsonism and essential tremor could also represent the co-occurrence of two common movement disorders.

Dystonic Tremor

Dystonic tremor usually occurs in a dystonic body part. Some distinguish this from "dystonia with tremor," tremor observed in an unaffected body part with dystonia elsewhere. Dystonic upper limb tremor will sometimes have a "null-point" where rotation of the affected limb will reach a point where the tremor is abolished. Like ET, dystonic tremor of the upper limbs will not have the latent period before reemerging on changing position as seen in IPD. Dystonic tremor tends to be more irregular and jerky in character and may have a torsional component.

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus (NPH) presents with one or all features of a triad of gait apraxia, urinary incontinence, and cognitive impairment. Gait can be similar to that of vascular parkinsonism because of involvement of periventricular descending corticospinal tracts. Imaging is essential in demonstrating dilatation of all ventricles out of proportion to the degree of cortical atrophy. Diagnosis is made most reliably by removal of a large volume (at least 40 mL) of cerebral spinal fluid (CSF) via lumbar puncture, which can also predict the potential for improvement with shunt placement although this remains controversial. Video of gait and cognitive assessment performed pre- and post-lumbar puncture is useful for later assessment.

The Role of Imaging in Diagnosing Parkinson's Disease

With a classical clinical picture, there is little or no role for neuroimaging in making a diagnosis of PD. Positron emission tomography (PET) with the fluorodopa ligand and single photon emission computed tomography (SPECT) are the principal options.

In SPECT studies, radioligands of the dopamine transporter (DAT) are used to determine the presynaptic integrity of nigrostriatal neurons. The DAT is exclusively localized to dopamine producing neurons. Advantages of the technique are the wide availability of SPECT scanners and the ability to continue dopaminergic medication at the time of imaging. Patients with IPD will demonstrate reduced radiotracer uptake in the striatum bilaterally, which tends to be asymmetrical, particularly affecting the posterior putamen (Fig. 5.2). Scans without evidence of dopaminergic dysfunction (SWEDDs) is the term applied to normal scans of patients with a clinical diagnosis of IPD. The diagnosis in these patients likely represents a false positive as no long-term data or postmortem studies have subsequently proven a diagnosis of IPD. Many of these patients will have a true diagnosis of essential or dystonic tremor, and some may have dopa-responsive dystonia, in which parkinsonism can be a feature.

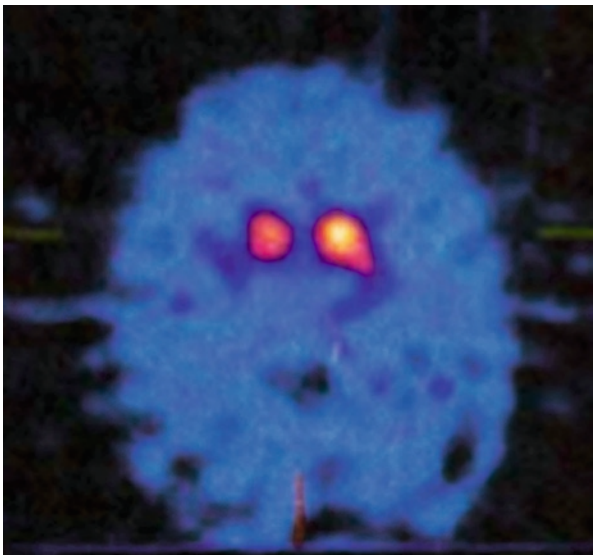


Fig. 5.2 Transaxial sections of an I-123 Ioflupane SPECT (DaTSCAN) from a patient with idiopathic Parkinson's disease demonstrating bilateral loss of uptake in the posterolateral aspect of the putamen bilaterally, more prominent on the rightside

SPECT imaging has no role in differentiating atypical parkinsonism from IPD, because both have reduced DAT imaging. Its main use is in differentiating IPD from ET, drug-induced tremor, or psychogenic tremor, all of which should have normal imaging. Transcranial sonography has emerged as an alternative imaging modality, with nigral hyperechogenicity having a sensitivity of up to 90% for IPD. Correlation with disease stage or severity has not been proven, and the significance of abnormalities in approximately 10% of clinically unaffected individuals has yet to be established.

Genetics

Case-control studies have confirmed a higher prevalence of IPD amongst first-degree relatives of affected patients supporting a genetic component to the disease. The relative contribution of environmental and genetic factors to the pathophysiology of idiopathic PD is unclear. A number of Mendelian single gene defects are associated with familial clustering of Parkinson's disease, although this accounts for less than 10% of all PD.

Familial PD has both clinical and pathological overlap with IPD but commonly has a younger age of onset. The first single gene mutation identified as a cause of familial PD was in the gene coding for α(alpha)-synuclein 14 years ago. There has been more recent interest in the study of common variants or single nucleotide polymorphisms (SNPs) in the genes associated with familial PD. Common variants may be associated with an increased

risk of sporadic PD although effect sizes are small and larger study populations are required to adequately power case-control studies. Some of the genes and their products associated with familial PD are discussed below.

α(Alpha)-Synuclein (Park 1)

The *SNCA* gene encoding the α(*alpha*)-synuclein protein is located on chromosome 4q21.3. α(*alpha*)-synuclein is an abundant presynaptic protein of unclear function. The resulting parkinsonism transmits in an autosomal dominant pattern. It is rare, being reported only in a few families in Greece, Italy, Germany, and Spain. The protein, α(*alpha*)-synuclein, is present in Lewy bodies. Duplication and triplication of the α(*alpha*)-synuclein gene also causes familial parkinsonism (PARK4), revealing that over-expression of the normal (wild-type) synuclein protein is sufficient to provoke dopaminergic neurodegeneration. This supports a pathogenic role for α(*alpha*)-synuclein in IPD. There is debate as to whether Lewy bodies are contributing to the pathogenesis of PD or if the aggregation of α(*alpha*)-synuclein fibrils to form Lewy bodies is an effort of the cell trying to protect itself from toxic α(*alpha*)-synuclein oligomers.

Parkin (Park 2)

The Parkin gene is found on chromosome 6q25.2–27 and is the most common genetic cause for early onset PD (before age 50), accounting for 50% of familial and 20% of sporadic early onset disease. *Parkin* mutations give rise to autosomal recessive PD that can have typical features of IPD, but may also demonstrate hyperreflexia, dystonia at presentation, and sleep benefit. Rest tremor is not prominent. Postmortem studies have shown nigral degeneration in patients with *Parkin* mutations but without Lewy bodies in most reported cases.

Pink1 (Park 6)

After *parkin* mutations, *PINK1* mutations are the second most common cause of early onset PD, sharing autosomal recessive inheritance. Disease progression is usually slow with early levodopa-induced dyskinesias. The *PINK1* gene codes for a mitochondrial protein that is a recognized component of Lewy bodies seen in late-onset IPD, and the few available autopsy studies have identified typical neuropathological findings.

DJ-1 (Park 7)

Mutations in the *DJ-1* account for 1–2% cases of early onset familial PD. The presentation is with a typical early onset parkinsonism, often with dystonic and neuropsychiatric features. Unlike the unaffected heterozygous state with Parkin and PINK1 mutations, carriers do not demonstrate functional neuroimaging evidence of nigrostriatal dysfunction.

LRRK2 (Park 8)

PARK8 is mapped to chromosome 12q12 and encodes for a previously unknown protein named leucine-rich repeat kinase-2 (*LRRK2*), ubiquitously expressed in the CNS. Seven pathogenic *LRRK2* mutations have been found, and are the most frequent genetic cause of familial PD. They account for up to 5% of sporadic PD in the Caucasian population. In Ashkenazi Jews and North African Berber Arabs, *LRRK2* mutations have been found in up to 20–40% of both familial and sporadic cases of PD. The most prominent mutation in the Caucasian population is the G2019S substitution. *LRRK2* mutations result in an autosomal-dominant parkinsonism that resembles typical late-onset IPD. Cognitive impairment is usually not a feature. Although the neuropathology associated to *LRRK2* mutations is highly variable, degeneration of substantia nigra neurons has been consistently observed.

Others

Glucocerebrosidase (GBA) gene mutations, when homozygous, cause autosomal recessive Gaucher's disease. Heterozygous carriers are at increased risk of developing parkinsonism that is indistinguishable from IPD. Up to 30% of Ashkenazi Jews with PD have been found to have this mutation; the mutation causes PD in other ethnic groups as well. Dopa-responsive dystonia may present during adulthood as slowly progressive parkinsonism and tends to respond to low doses of levodopa. Parkinsonism can also be a predominant feature of the Westphal variant of Huntington's disease, although this is usually in juvenile patients and family history should be informative. Some forms of spinocerebellar ataxia (SCA2 and SCA3) can present with a levodopa-responsive parkinsonism with minimal cerebellar features.

Clinical Features

Motor

Rest Tremor

Rest tremor, typically of 4–5 Hz, is the first symptom recognized in 70% of patients, but may be absent in 20%. The classic "pill-rolling" tremor involves the thumb and forefinger. Rest tremor disappears with action but reemerges after a latent period of seconds as the limbs maintain a posture (*reemergent tremor*). Tremor increases with walking (a possible early sign), stress, or excitement. Tremor is also common in the lips, chin, and tongue but not the head.

Bradykinesia with Decrement

Bradykinesia encompasses slowness of movement, difficulty initiating movement, and loss of automatic movement. Decrement refers to a reduction in amplitude of movement, particularly with repetitive movements. Often, different tactics need to be used by the examiner

to bring out bradykinesia that might only be seen during certain actions, such as finger tapping, pronation–suppination movements, or opening and closing the fists. The face loses spontaneous expression (*hypomimia*) with decreased frequency of blinking. Speech becomes soft (*hypophonia*), and the voice has a monotonous tone with a lack of inflection (*aprosody*). Some patients do not enunciate clearly (*dysarthria*) and do not separate syllables clearly, thus running the words together (*tachyphemia*) and others stutter (*palilalia*). Bradykinesia of the dominant hand results in small and slow handwriting (*micrographia*). Difficulty rising from a deep chair, getting out of cars, and turning in bed are symptoms of truncal bradykinesia. Subtle signs of bradykinesia can be detected if one examines for slowness in shrugging the shoulders, smiling, lack of gesturing in conversation, and decreased blink frequency. Walking is slow, with a shortened stride length and a tendency to shuffle with decreased heel strike; arm swing decreases and eventually is lost.

Rigidity

Rigidity is an increase of muscle tone on passive movement and is not velocity dependent as seen with spasticity. Resistance is equal in all directions and usually has a "cogwheeling" character caused by the underlying tremor even if not visible. Rigidity of the passive limb increases while another limb is engaged in voluntary active movement, also known as the co-activation or facilitation test. Axial rigidity at the neck can similarly be accentuated by asking the patient to open and close both hands. Mild upper limb rigidity can be elicited by standing behind the patient and rocking their shoulders back and forward to produce passive arm swing that will be reduced on the more affected side.

Loss of Postural Reflexes

Loss of postural reflexes leads to falling and eventually to an inability to stand unassisted. These reflexes are tested by the pull-test during which the examiner, who stands behind the patient, gives a sudden firm pull on the shoulders after explanation of the procedure, and checks for *retropulsion*. With advance warning, an unaffected person can recover within two steps.

Flexed Posture

This commonly begins in the elbows and spreads to involve the entire body. The head is bowed, the trunk is bent forward, the back is kyphotic, and the arms are held in front of the body with the elbows, hips, and knees flexed. Walking is marked by *festination*, whereby the patient walks faster and faster with short steps, trying to move the feet forward to be under the flexed body's center of gravity to prevent falling. Deformities of the hands include ulnar deviation, flexion of the metacarpophalangeal joints, and extension of the interphalangeal joints (*striatal hand*). The hallux may be dorsiflexed (*striatal toe*). Lateral tilting of the trunk can develop, and extreme flexion of the trunk (*camptocormia*) is sometimes seen, which should be abolished when lying flat.

Freezing

This manifests as the transient inability to perform active movements. Freezing occurs suddenly and is transient, usually lasting seconds. It will typically occur when the patient begins to walk (*start hesitation*), attempts to turn while walking, or (approaches) a destination, such as a chair in which to sit (*destination hesitation*). Tight spaces can also provoke freezing, such as doorways, as can time-restricted activities such as crossing heavily trafficked streets or answering the phone. The combination of freezing and loss of postural reflexes is particularly devastating, and a common cause of falls.

Non-motor Symptoms

Later in the clinical course, non-motor and axial motor symptoms become prominent and account for greater disability, being poorly responsive to dopaminergic treatment (Table 5.4). After 20 years of disease in the Sydney Multicentre Study, falls were experienced by 87%, moderate dysarthria in 81%, dementia in 84%, visual hallucinations in 74%, postural hypotension in 48%, and urinary incontinence in 71%. Some non-motor symptoms can be observed as "pre-motor" phenomena, appearing before typical motor features. These include constipation, rapid-eye-movement (REM) sleep behavior disorder, olfactory impairment, and mood disorders. Some of the more troublesome problems and their management are discussed below.

Autonomic Involvement

Constipation

Constipation is almost universal in PD and can influence the efficacy of oral therapies by causing erratic absorption. Treatment with a regular stool softener, sometimes combined with a stimulant laxative is usually effective and most patients will require a regular laxative. The use of abdominal plain films can guide the use of laxatives and should be considered in patients whose motor control has deteriorated or where response to levodopa is variable.

Dysphagia

Dysphagia is not uncommon. Rarely recurrent aspiration pneumonia can complicate late stages of the disease. Patients benefit from access to a speech and language therapist to teach strategies to improve swallowing. Dysphagia is not typically levodopa responsive and can deteriorate after deep brain stimulation. A dry oropharyngeal mucous membrane due to anticholinergic agents is one readily treatable cause of swallowing impairment.

Table 5.4 Non-motor symptoms in Parkinson's disease

Neuropsychiatric • Depression • Anxiety, panic attacks • Hallucinations, illusions, delusions • Dementia, mild cognitive impairment • Obsessional, repetitive behaviors[a] • Delirium[a] • Anhedonia
Autonomic symptoms • Orthostatic hypotension • Nocturia, urgency, frequency • Paroxysmal sweating • Seborrhea • Erectile impotence • Xerostomia
Gastrointestinal • Ageusia • Sialorrhea • Nausea and vomiting • Dysphagia • Constipation • Incontinence
Sensory symptoms • Pain (can be pseudoradicular) • Paresthesia • Olfactory disturbance • Visual blurring
Sleep disorders • REM sleep behavior disorder • Difficulty initiating or returning to sleep, insomnia • Restless legs syndrome • Periodic limb movements in sleep • Vivid dreaming • Nocturnal hallucinations • Excessive daytime somnolence
Others • Fatigue • Seborrhea • Weight loss or gain[a]

[a]May be drug related

Sialorrhea

This is a manifestation of reduced swallow frequency in IPD as opposed to excessive saliva production. Anticholinergics are effective, but most available agents are tertiary amines that enter the CNS and can impair memory or cause hallucinations in older patients. Quaternary amines do not penetrate the CNS and are preferable. Sublingual 1% atropine can be used with some success. Injections of botulinum toxin into the salivary glands can be attempted. Pharyngeal weakness due to local toxin diffusion is a potential complication but is rarely encountered with dry mouth being a more common side effect.

Orthostatic Hypotension

Orthostatic hypotension (OH) can cause significant morbidity and contributes to the risk of falling. Conservative measures such as increased fluid intake, additional dietary salt, avoidance of hot baths and large meals, and the use of compression stockings can help. More resistant symptoms can respond to the sympathomimetic midodrine, starting with 5 mg and titrating up to three doses of 10 mg a day if necessary. Fludrocortisone can be used, typically starting at 0.1 mg/day. Supine hypertension can result from increased salt and mineralocorticoid ingestion. Elevation of the top of the bed to 30° at night can help this by reducing renal mineralcorticoid production. OH can be aggravated by dopaminergic therapy (dopamine agonists in particular), dehydration, and constipation.

Urinary Symptoms

Detrusor hyperreflexia predominates in IPD, causing frequency, urge, nocturia, and sometimes incontinence. In older male patients, the picture may be mixed with prostatism and anticholinergics are ideally prescribed after bladder ultrasound to determine residual volume, avoiding exacerbation of preexisting outflow obstruction. Equally important is the propensity of these agents to cause cognitive impairment in older patients with IPD, in particular the tertiary amines that cross the blood-brain barrier.

Trospium chloride is a quaternary amine that may have a better side effect profile although there is little trial data available addressing this issue. Reduction in late-night fluid intake can help nocturia. In patients treated for OH, nocturia can occur as a result of nocturnal pressure natriuresis secondary to supine hypertension.

Sexual Dysfunction

Sexual dysfunction is more commonly encountered in IPD than in the general population. Men with erectile dysfunction can be treated with agents such as sildenafil (this can exacerbate OH). Female patients may report reduced libido and conversely hypersexuality can

occur with dopamine agonist treatment as a manifestation of an impulse control disorder (discussed later).

Pain

Pain is not uncommon and can vary from uncomfortable paraesthesias to nociceptive or neuropathic sounding pain. Patients can initially present with pain in a joint on the symptomatic side, typically a shoulder, probably due to hypokinesis and immobility. Adequate treatment and physiotherapy can improve this considerably. Some patients complain of pain down one side of their body or in an apparently radicular distribution, both of which will respond to levodopa suggesting a central dopamine deficit as the underlying cause. True radiculopathies from nerve root compression can also worsen in the "off" state. Restless legs syndrome can be seen in association with IPD and can give rise to an aching discomfort in the legs at night, which can improve with a low dose of a dopamine agonist taken at night.

Abnormal Sweating

The pathophysiology of abnormal sweating in IPD is unclear but Lewy body pathology involving the hypothalamus may be contributory. Sympathetic cholinergic fibers are the final common pathway, which mediate the sweating response although dopamine would appear to play a role, as excessive sweating of the head and upper body can occur as an "off" phenomenon, often in bed at night. Sweating can also occur in the context of dyskinesias, but is usually less prominent than the paroxysmal attacks of drenching sweats reported in "off" periods. Other causes of excessive nocturnal sweating should be considered including thyrotoxicosis and latent tuberculosis infection.

Sleep Disturbance and Daytime Somnolence

Sleep disruption is common and multifactorial in IPD. Patients experience difficulty initiating sleep, fragmented sleep, REM sleep behavior disorder (RBD) and inversion of the sleep–wake cycle. RBD can predate the clinical onset of IPD. Sleep disruption can exacerbate the *e*xcessive daytime somnolence that is both associated with the disease itself and dopaminergics.

Sleep disruption in IPD probably relates to degeneration of brainstem nuclei that regulate the balance between sleeping and waking states. The pedunculopontine and subcoeruleal nuclei are thought to play a role in maintaining the normal muscle atonia of REM that is lost in RBD. Involvement of nondopaminergic nuclei important in maintaining arousal including the raphe nuclei (serotonin), locus coeruleus (noradrenaline), the tuberomamillary nucleus (histamine) may account for daytime somnolence. The burden on bed partners can be significant. Factors contributing to sleep disruption and therapies are given in (Table 5.5).

Table 5.5 Causes and treatment of sleep disturbance in Parkinson's disease

Bradykinesia and rigidity	Can make it difficult to turn in bed to find a comfortable position. Contribute to difficulty initiating sleep or returning to sleep after an arousal. Some patients overcome this by using satin sheets and night-clothes to facilitate movement.
Restless legs syndrome (RLS)	Will respond to dopamine agonists and levodopa preparations given late at night. Treatment can be complicated by augmentation whereby symptoms become longer lasting, more severe, and more extensive. It is important to ensure dyskinesias are not the cause of disturbed sleep as increased dopaminergic treatment will exacerbate this. Opioids, such as propoxyphene, can often suppress RLS and not cause augmentation.
Periodic limb movements in sleep	Periodic episodes of rhythmic extension of the hallux with dorsiflexion of the ankle, sometimes extending proximally to involve knee and hip flexors. Commonly associated with RLS and can also respond to dopaminergic drugs. Opioids can also be of benefit in resistant cases. Propoxyphene 65 mg late in the day before the onset of symptoms is usually effective. Start with a half-tablet, and titrate up to two tablets if necessary.
Nocturia	Common in this age group. Anticholinergics can help but may exacerbate vivid dreams or hallucinations. Sometimes responds to dopaminergic treatment. Rule out coexisting pathology with referral to urology for assessment where appropriate.
Vivid dreams	Are usually not disruptive to sleep but can be upsetting. Can resolve with a reduction in dopaminergic or anticholinergic drugs taken at night. Can be exacerbated by amphetamine metabolites of selegiline, which should be taken early in the day. Low-dose quetiapine, starting at 12.5–25 mg at night, can help if required.
Nocturnal hallucinations	Are associated with cognitive impairment in IPD and along with vivid dreams can respond to a low dose of quetiapine that can also improve insomnia due to its soporific effects. Donepezil 5–10 mg nocte can also be helpful.
REM sleep behavior disorder (RBD)	Semi-purposeful movements in sleep, typically as if kicking or fighting off an attacker. Occurs as a consequence of losing normal physiological paralysis during REM sleep. RBD is typically reported by bed partners who should be questioned. A small dose of clonazepam, 0.25–1 mg at night, can be very effective. Melatonin, 3–12 mg at night, is an alternative when clonazepam exacerbates daytime somnolence and is generally well tolerated.
Insomnia or early morning wakening	Can be markers for underlying depression. Tricyclic antidepressants such as amitriptyline may have a role in this setting to improve mood and produce a hypnotic effect (use with caution in patients taking an MAO-B inhibitor). Drugs that may be interfering with sleep such as selegiline or modafinil should be withdrawn or taken early in the day to minimize their stimulant effect. There is no specific contraindication to the use of benzodiazepines as night sedation although any "carry-over" into the next day can affect cognition and increase risk of falling.
Sleep disordered breathing	May be (due to sleep apnoea) and important to consider as treatment with noninvasive ventilatory support at night can be very effective. May not always have the typical body habitus seen in obstructive sleep apnea.

Neuropsychiatric

Parkinson's Disease and Dementia

Dementia is not typically an early feature of PD and if evident within 1 year of presentation, a diagnosis of dementia with Lewy bodies (DLB) is made, otherwise the term Parkinson's disease and dementia (PD–D) is used. The overall prevalence of dementia in PD is high at approximately 40%, increasing in frequency with advancing years. The risk of developing dementia is 2.8-fold greater than controls.

The pathological substrate of dementia in PD remains uncertain. The involvement of subcortical structures, in particular the medial nigra and thalamus, may be important but cortical Lewy body burden and co-existent Alzheimer's disease pathology have also been shown to correlate with cognitive impairment. Cholinergic cell loss is more severe than that seen in Alzheimer's disease with severe neuronal loss in the basal nucleus of Meynert. The relative contribution of noradrenergic, dopaminergic, and serotonergic neurons to PD–D is unknown.

The hallmark of cognitive impairment in IPD is executive dysfunction with impaired inability to plan, organize, or regulate internally generated goal-directed behavior. Memory impairment is not as prominent as in Alzheimer's disease (AD) although responses can be slow (*bradyphrenia)*. Memory deficits usually improve with prompting, suggesting a problem with memory retrieval rather than encoding. Verbal fluency and visuospatial function may also be affected. Hallucinations are more common than in AD, present in up to 70% of patients.

Once infectious and drug-related confusional states have been out-ruled, treatment with a cholinesterase inhibitor should be considered. Both rivastigmine and donepezil are effective for cognitive and behavioral symptoms without worsening parkinsonism, although tremor can worsen. Hallucinations can respond to cholinesterase inhibitors, but if antipsychotics are sometimes required, clozapine or quetiapine can be used although controlled trials are lacking. Clozapine is associated with a low risk of agranulocytosis (1–2%), so baseline full blood count with subsequent monitoring is required; weekly initially for at least 18 weeks with local guidelines being followed thereafter. Treatment is started at 6.25 mg at bedtime and gradually titrated to response to 25–75 mg per day. Quetiapine may be less effective than clozapine although it is generally used first as it is not associated with hematological adverse effects. It is usually started at 12.5–25 mg at bedtime. Other atypical neuroleptics, risperidone, olanzapine, and aripiprazole have all been associated with worsening of parkinsonism. There is insufficient evidence to recommend use of the glutamate antagonist memantine in PD–D.

Depression

Prevalence data for depression in IPD varies and is dependent on diagnostic criteria. Depressive symptoms often go undiagnosed, with hypophonia, poor sleep pattern, and flattened affect being more commonly attributed to parkinsonism. Depression in IPD has a higher prevalence than in other chronic, incapacitating illnesses suggesting an endogenous

component. This has been attributed to global monoamine depletion in IPD, in particular that involving noradrenergic neurons. Dopamine receptors are likely to play a role in regulation of mood. SSRI agents reduce dopamine uptake in the prefrontal cortex and chronic treatment leads to changes in D2/D3 receptor sensitivity in the nucleus accumbens.

SSRIs are commonly prescribed for depression in IPD. They are well tolerated but have a theoretical risk of inducing a serotonin syndrome when administered with an MAO-B inhibitor. This does not seem to be relevant with the doses used in clinical practice. Agents targeting dopaminergic and noradrenergic systems may be superior.

The tricyclic antidepressants desipramine (25–50 mg nocte) and nortriptyline (20–40 mg nocte) inhibit noradrenaline uptake and have a better side effect profile than amitriptyline due to less anticholinergic activity. Nortriptyline was found to be more effective than slow release paroxetine in one randomized double-blinded trial. The dopamine agonists, pramipexole and ropinirole, have been also shown to be effective. The effect appears to be independent of any effect on motor function and may relate to an effect on limbic D2/D3 receptors.

Anxiety

Anxiety is a known preclinical risk factor for IPD, suggesting that, in at least some patients, it is a disease phenomenon and not a reaction to it. Panic attacks can occur in "off" states and can be managed by minimizing motor fluctuations and "off" time. It is important to be aware that manic and anxiety states have been reported following dopamine agonist treatment. Some patients benefit from the short-acting benzodiazepines alprazolam (0.25–1 mg TID) and lorazepam (0.5–1.0 mg TID). Tricyclic antidepressants or SSRIs are sometimes required where there is additional depression (see section above).

Apathy

Apathy is characterized by a reduction in goal-directed behavior and is thought to be related to executive dysfunction in IPD. Disturbance of striato-frontal circuitry may be important. Dopaminergic reward pathways between the midbrain and limbic cortex are affected in IPD. Patients may not report depressive symptoms and typically will not share the frustration of caregivers with respect to their lack of motivation and drive. Stimulants such as modafinil are sometimes effective and empirical use of dopaminergics may help. A broader approach increasing monoamine transmission with SSRIs, SNRIs, and TCAs can also be used.

Treatment of Motor Symptoms: Overview

Treatment must be tailored to the individual patient; each with a unique set of symptoms, different functional requirements, and responding differently to various treatments. The goal is to maintain independence for as long as possible while attempting to address motor

and non-motor symptoms of the disease. Because no treatment has been shown unequivocally to have a neuroprotective effect (discussed later), pharmacological treatment in the early stages is focused on symptomatic management. Levodopa is the most effective oral treatment for bradykinesia and rigidity. Much of the therapeutic effort in advanced disease involves control of the complications associated with chronic levodopa use, namely, fluctuations, dyskinesias, and increasingly recognized neuropsychiatric aspects. Importance has therefore been placed on the timing of levodopa introduction, particularly in younger patients who have longer to live with dyskinesias, should they develop. Advanced IPD is characterized by these treatment complications, non-motor symptoms, and motor symptoms that are not levodopa responsive. Non-pharmacological treatments, in particular physiotherapy, have a significant role. Physiotherapy involves patients in their own care, promotes exercise, keeps muscles active, and preserves mobility. This approach is particularly important as IPD advances because many patients will tend to remain sitting and inactive, exacerbating their immobility.

Symptomatic Treatment of Motor Symptoms

Levodopa

Dopamine is unable to cross the blood-brain barrier, but its precursor levodopa is and remains the most effective oral therapy. Early concerns that levodopa might be toxic to dopaminergic neurons proved to be unfounded and with respect to the pre-levodopa era, mortality and morbidity rates in PD have fallen. Dopamine has a strong effect on the area postrema, a fourth ventricular structure with high density of dopamine receptors and without protection from the blood-brain barrier. Nausea and vomiting are therefore common side effects.

Levodopa is routinely administered with a dopadecarboxylase inhibitor (carbidopa or benserazide) to prevent its peripheral breakdown to dopamine; these agents do not penetrate the blood-brain barrier. They potentiate the effects of levodopa, allowing about a fourfold reduction in dose to obtain the same benefit. Approximately 75 mg to 100 mg of carbidopa is required to completely suppress peripheral dopadecarboxylase. Some formulations contain additional carbidopa if this is an issue; Sinemet Plus combines 25 mg of carbidopa with 100 mg of levodopa instead of the 10 mg in Sinemet 110. Additional carbidopa can also be prescribed in 25 mg tablets. Domperidone is preferred if an antiemetic is required. Unlike prochlorperazine and metoclopramide, it does not cross the blood-brain barrier and will not therefore exacerbate parkinsonism. Domperidone is not available in the United States where trimethobenzamide hydrochloride (Tigan) can be used instead. Domperidone (Motilium) should be taken 30 min before each dose and can usually be discontinued gradually within weeks. Other common side effects reported when initiating levodopa treatment include orthostatic hypotension, confusion, hallucinations, and sedation.

Levodopa is available in a number of forms and doses that allow treatment to be tailored to the individual needs of each patient. Sinemet (levodopa/carbidopa) is available in strengths of 50/12.5 mg, 100/10 mg, 100/25 mg and 225/50 mg. Madopar (levodopa/benserazide) is only available in Europe and in strengths of 100/25 mg and 50/200 mg.

There is also a water-dispersible formulation of Madopar (50/12.5 mg and 100/25 mg) with a more rapid onset and shorter duration of action. In practice, doses over 1,200 mg daily are not often used.

Levodopa, carbidopa, and the COMT inhibitor entacapone are available in a single tablet (Stalevo). This comes in a number of strengths of levodopa (50, 75, 100, 125, 150, and 200 mg), each combined with 200 mg of entacapone. This reduces the total number of tablets taken daily and reduces "off" time in patients experiencing the wearing-off phenomenon. Entacapone prolongs the half-life of levodopa from 90 min to approximately 180 min. It was thought that concurrent entacapone may reduce the pulsatile stimulation of dopamine receptors and avoid levodopa-induced dyskinesias, but a clinical trial showed the opposite effect; there were earlier and more severe dyskinesias when concurrent entacapone was utilized when levodopa therapy was started.

Both Sinemet and Madopar are available in modified release formulations that are sometimes used to smooth-out motor fluctuations or for nighttime symptoms. Onset of action can be delayed and bioavailability is approximately 75% of standard release formulations because the entire content of the extended-release formulation is not absorbed before the tablet passes the duodenum and jejunum (the sites where levodopa is absorbed).

Dopamine Agonists

Dopamine agonists (DA) directly stimulate dopamine receptors and are not reliant on degenerating striatal nerve terminals for uptake and conversion into an active product. For most patients, DA are effective as a monotherapy in the early stage of the disease, allowing later introduction of levodopa and thus delaying motor complications. Dopamine agonists will rarely induce dyskinesia but are less effective for the symptomatic management of IPD; most patients require the addition of levodopa within a few years. Dopamine agonists do not delay the time to onset of dyskinesias once levodopa is added when compared with patients starting on levodopa from the outset.

The earliest DA in use were the ergot derivatives bromocriptine, pergolide, lisuride, and cabergoline. Retroperitoneal, pleural, and pericardial fibrosis, and restrictive fibrotic valvulopathy were reported with pergolide and cabergoline, attributed to the activation of the $5HT_{2B}$ receptor. Pergolide is no longer available in the U.S. Lisuride, a short-acting ergoline agonist given subcutaneously is not associated with fibrotic complications ($5HT_{2B}$ antagonist), but has never been in common usage due to the emergence of apomorphine.

The non-ergoline agonists, pramipexole, ropinirole, and rotigotine are currently the most frequently prescribed oral DA. Pramipexole and ropinirole are available in multiple daily dosing formulations and more recently in modified release formulations taken once daily. These formulations may have benefits in improving compliance and nocturnal or early morning symptoms. Rotigotine is administered transdermally, avoiding delays of gastric motility, first-pass metabolism, and competition with dietary protein. Skin site reactions are relatively common but mild, occurring in up to 40% of patients. Typical initiation, maintenance, and maximum doses for the non-ergoline DA are given in Table 5.6. The clinical response to pramipexole at doses greater than 0.7 mg TID may not be greater

Table 5.6 Commonly used nonergot dopamine agonists and typical dose schedules

Dopamine agonist	Start dose (mg)	Week 2 (mg)	Week 3 (mg)	Week 4 (mg)	Therapeutic range mg/24 h	Max dose
Ropinirole	0.25 TID	0.5 TID	0.75 TID	1.0 TID	9.0–12.0	8 mg TID
Pramipexole (salt)	0.88 TID	0.18 TID	0.36 TID	0.7 TID	0.36–0.7	1.08 mg TID
Rotigotine	2	4	6	8	4.0–8.0	16 mg/24 h

than that at lower doses although side effects will be more frequent. Conversely, ropinirole is often not titrated quickly enough to an effective treatment dose (minimum of 3 mg TID) due to its low initiation dose. Rotigotine should be titrated straight up to 8 mg/24 h if tolerated whether as a monotherapy or in combination with levodopa. Dose increases are then in 2 mg increments at weekly intervals until a satisfactory response is obtained.

Dopamine agonists have a less favorable side effect profile than levodopa and are more likely to cause confusion, hallucinations, nausea, postural hypotension, and ankle edema. Some patients may idiosyncratically have a better tolerance for one agonist over another. Much attention has been paid to reports of sudden unheralded episodes of sleep or "sleep attacks" with DA. Daytime somnolence is a common problem in IPD. Further study of this phenomenon suggests that these "sleep attacks" may represent unintended sleep episodes in individuals with excessive daytime somnolence from disturbed sleep and dopaminergic treatment. Tolerance to the feeling of chronic sleepiness and memory impairment may give the impression of sudden "attacks" of sleep. The soporific effect of dopaminergic therapy would appear to be the same whether dopamine agonist or levodopa is prescribed. Nonetheless, patients on DA, who are driving and reporting frequent unintended and reportedly unpredictable episodes of sleep, should have their dose reduced and be advised not to drive until there is improvement.

Monoamine Oxidase Type B (MAO-B) Inhibitors

Selegiline and rasagiline are irreversible MAO-B inhibitors that have a mild symptomatic effect. MAO-B is an enzyme responsible for the central clearance of dopamine, and its inhibition augments the effect of levodopa. Both drugs can be used for the management of symptoms in early IPD or as an adjunct to levodopa to reduce "off" time during motor fluctuations. As a monotherapy, selegiline can delay the need for levodopa by an average of 9 months. Selegiline has few adverse effects when given alone. When given concurrently with levodopa, it can increase the dopaminergic effect causing dyskinesias and hallucinations. Selegiline has amphetamine metabolites that can disturb sleep if given late at night. A dose of 5 mg once or twice daily, ideally before midday, is typically used. Above 10 mg, selectivity for MAO-B is lost, risking a sympathetic crisis. Rasagiline, 1 mg once daily, is a second-generation irreversible MAO-B inhibitor providing a stronger symptomatic effect. It has no amphetamine-like breakdown products and may be associated with less sleep disturbance.

Amantadine

Amantadine is a mild indirect dopaminergic agent that augments dopamine release. It also has some anticholinergic and antiglutamatergic properties. Amantadine is now uncommonly used in the treatment of early IPD due to the availability of other symptomatic treatments with better side effect profiles. In advanced IPD, amantadine is used for its antidyskinetic effect, possibly as a result of its glutamate antagonism. Unfortunately, patients will often report a falloff of benefit after several months. Adverse effects include livedo reticularis (a reddish mottling of skin) on the legs, dry mouth, ankle and leg edema, postural hypotension, visual hallucinosis, and nightmares. Amantadine has a long half-life of about 12 h, and if side effects occur, it can be stopped abruptly. The usual dose is 100 mg two times per day, but sometimes a higher dose (up to 200 mg twice daily) may be required for dyskinesias.

Anticholinergic (Antimuscarinic) Drugs

Anticholinergic agents are less effective antiparkinsonian agents than are dopaminergic drugs (estimated to improve parkinsonism by about 20%), but can be a more effective treatment for tremor. Their exact mechanism of action is unknown; they may redress an imbalance between cholinergic and dopaminergic transmission in IPD. Trihexyphenidyl is a widely used anticholinergic agent. A common starting dose is 2 mg TID. It can be gradually increased to 15 mg or more per day although doses as high as this are rarely tolerated. Biperedin and procyclidine are alternatives.

Adverse effects are common with many patients reporting poor short-term memory. All patients should have a baseline cognitive assessment performed before starting treatment. These agents are preferably avoided if a patient or relative report prior memory impairment. Occasionally, hallucinations and psychosis occur, particularly in the elderly; these drugs should therefore, as a rule, be avoided in patients older than 65 years of age, although this is best judged on "biological age." In older patients, amitriptyline or diphenhydramine are sometimes beneficial, without the central side effects of more potent anticholinergic agents and can also be used as a hypnotic. Anticholinergics can reduce sialorrhea when tolerated. Peripheral side effects are common, including dry mouth, blurred vision, constipation, and urinary retention. One approach is to treat these adverse effects by appropriate antidotes instead of discontinuation. Pilocarpine eye drops can overcome dilated pupils that can cause blurred vision, and can be useful if glaucoma is present. Pyridostigmine, up to 60 mg TID, can help to overcome dry mouth, urinary difficulties, and constipation.

COMT Inhibitors

When levodopa is administered with a dopa decarboxylase inhibitor, cathchol-O-methyltransferase (COMT) then becomes the main enzyme responsible for its breakdown in the periphery. COMT inhibitors prolong the pharmacological effect of levodopa, doubling its elimination half-life and augmenting its peak dose effect. They are useful in

managing end of dose deterioration and reducing "off" time but may exacerbate peak-dose dyskinesias resulting in a need to reduce individual levodopa doses by 15–30%. Entacapone and tolcapone are approved for use in IPD. Entacapone acts peripherally only and because it has a very short half-life, 200 mg is given with each dose of levodopa. A combined formulation with levodopa and carbidopa (Stalevo) has similar efficacy to these compounds administered separately. Tolcapone acts both centrally and peripherally. It is initially prescribed at 100 mg TID and is more potent than entacapone. It has been associated with liver enzyme elevations, and three deaths from hepatic failure occurred in patients not having regular monitoring. It is therefore regarded as a second-line agent. Regular monitoring of liver parameters should allow the drug to be used safely with immediate discontinuation if ALT or AST exceed the upper limit of normal.

Neuroprotection

No definitive evidence has been found of neuroprotection using any agent in IPD. There are a number of issues that need to be addressed before neuroprotective strategies in PD can be properly investigated:

1. Timing of neuroprotection: At presentation, the majority of nigrostriatal neurons have already been lost; therefore any neuroprotective agent may be too late to be effective. Studies of at-risk asymptomatic carriers of disease-causing genes (e.g., LRRK2) may prove useful in teasing out this issue. However, in some cases at least, familial PD may have a different disease mechanism to sporadic disease. Familial cases are also uncommon and age of onset and penetrance are variable, making interpretation difficult. The identification of preclinical markers in sporadic IPD is therefore of great interest.
2. It is quite possible that IPD represents a heterogeneous group of mechanisms giving rise to a final common phenotype. If this is so, the identification of a single effective neuroprotective agent will be difficult. Clarification of the pathophysiology of IPD will help target specific neuroprotective therapies tailored to one or more responsible mechanisms.
3. Outcome measures that satisfactorily measure neuroprotection are needed. Clinical markers do not necessarily correlate with disease modification, particularly when the agent being studied has symptomatic effects. In IPD, the Unified Parkinson's Disease Rating Scale (UPDRS) is commonly used. The patient scores non-motor domains but many are not included. These symptoms may be more important in assessing disease modification as they generally are not levodopa responsive and thus are unmodified by any symptomatic drug effect. The addition of imaging studies to assess striatal dopamine receptor density may be of value as a surrogate of neuronal loss.
4. Trial design is vital to allow interpretation of any findings. A "wash-out" design allows, in theory, the symptomatic effect of a drug to wear off and thus leaving only a putative neuroprotective effect to account for a group difference. The biological effect of

dopaminergic drugs may however last long beyond their pharmacological effect making interpretation difficult. "Delayed-start" trials have attempted to address this issue by starting one group of patients on a study drug before the other. Failure of the delayed-start group to "catch up" with the early start group supports a possible neuroprotective effect of early treatment. This approach also has potential flaws. If a beneficial effect takes a long time to become established, the delayed-start group may not have had sufficient exposure to the study drug, Also, a strong symptomatic effect can be sufficient to mask any disease-modifying effect.

Selected Trials of Interest

- Antioxidants have been investigated because the metabolism of dopamine by MAO-B produces free radicals. The DATATOP trial compared the effects of the MAO-B inhibitor selegiline (10 mg/day) and the antioxidant tocopherol or vitamin E (2,000 U/day). Selegiline delayed the requirement of levodopa by a mean of 9 months. Because of an unexpected symptomatic effect of selegiline, disease modification could not be proven. The subsequent trial with selegiline, the BLIND-DATE trial, added selegiline or placebo to patients already taking levodopa. The results showed less clinical worsening of UPDRS scores, less freezing of gait, and a lesser increase of additional levodopa in the group taking selegiline compared to the placebo group despite the liberty to take as much levodopa as needed. This supports the possibility of disease modification but doesn't prove it.
- The recent ADAGIO trial attempted to readdress the question by studying a different MAO-B inhibitor, rasagiline (1 mg or 2 mg), versus placebo using a delayed start protocol. The delayed start group demonstrated significant differences in UPDRS (1.7 points) with respect to the 1 mg dose of rasagiline at the end of 52 weeks. Questions remain, however, as strangely, the findings using a 1 mg dose were not replicated in the group receiving 2 mg.
- Coenzyme Q10, an antioxidant and mitochondrial-active agent, at 1,200 mg/day showed some reduction of parkinsonism in a randomized, placebo-controlled, double-blind pilot study of 80 patients not requiring treatment for their disability. The trial met prespecified criteria looking for a linear response between dose and change in UPDRS ($p = 0.09$). The placebo group and patient group receiving 1,200 mg differed significantly with respect to this change (+11.99 vs. +6.69, respectively). A larger Phase III trial of coenzyme Q10 is in progress.
- The ELLDOPA study was designed to determine if levodopa has a toxic effect on dopaminergic neurons. A placebo group was compared with three groups receiving levodopa at varying doses, 150 mg, 300 mg, and 600 mg per day. All subjects had early PD (less than 3 years). Treatment was for 40 weeks with a 2 week washout period before final assessment. The placebo group UPDRS worsened after 42 weeks while the high-dose levodopa group maintained their improvement of −1.4 points with respect to baseline. This result raised the question of a neuroprotective effect of levodopa; however, the improvement could be due to a prolonged symptomatic effect insufficiently washed out over 2 weeks.

Treatment According to the Stage of Parkinson's Disease

When and How Should Treatment Be Started in Early Stage Disease?

In the absence of definitive evidence favoring a disease-modifying drug, authorities in the past have generally agreed that treatment is not necessary when symptoms are not causing disability. This practice was motivated by a desire to avoid unnecessary side effects that might outweigh a small benefit.

With the advent of newer agents that may have a disease-modifying role, some consider that initiation of treatment at the time of diagnosis is warranted to slow degeneration in an already considerably depleted substantia nigra. It is proposed that dopamine depletion in the basal ganglia leads to maladaptive, compensatory changes within basal ganglia circuits, which may also put additional metabolic stress on a failing system. Early symptomatic treatment might prevent or delay decomposition by normalizing basal ganglia function. This hypothesis is based on the apparent benefit of early treatment demonstrated in trials of drugs that all have some symptomatic benefit, including levodopa, selegiline, and rasagiline. This was examined in the recent PROUD study, which assessed early versus delayed start pramipexole. No difference was found between early and delayed treatment groups.

Many neurologists will now empirically start with either selegiline or rasagiline monotherapy, providing well-tolerated, once daily dosing with mild symptomatic benefit before starting more potent dopaminergic drugs or an anticholinergic for tremor predominant disease. The next step is typically the addition of a dopamine agonist (especially in young patients more prone to develop dyskinesias) due to their low propensity to induce dyskinesias and their ability to provide early symptom control in most patients.

Stage When Symptoms and Signs Require Treatment with Levodopa

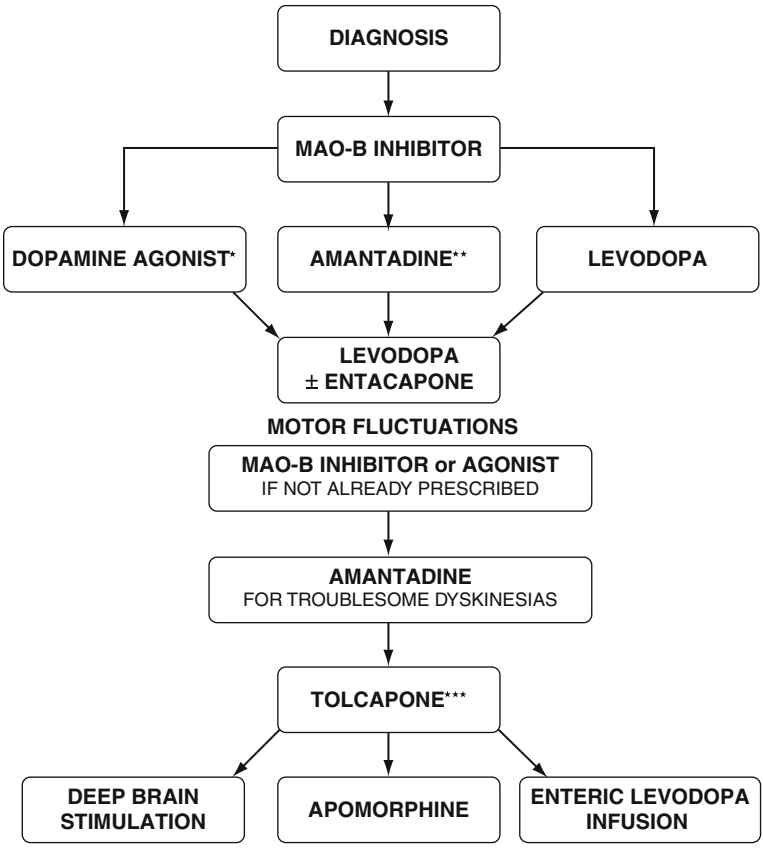
Incremental addition of dopamine follows when symptom control is no longer adequate. Levodopa can be introduced as a first-line agent in treatment-naïve patients, but this approach is usually reserved for older patients (>70 years of age, e.g.), patients with cognitive impairment in whom a greater risk of neuropsychiatric complications with DA could be expected, or when a patient is at a high risk of injury due to falls.

The conflict exists between the development of dyskinesias after chronic levodopa treatment and its superior efficacy and tolerability when compared to dopamine agonists. After 5 years of levodopa therapy, about 75% of patients will have some form of motor complication. Those in favor of early levodopa point out the relatively poor tolerability of DA and better quality of life scores with early levodopa compared to those started on an agonist. They also highlight follow-up of these two groups showing that only mild dyskinesias are significantly more frequent in those receiving levodopa ab initio. Furthermore, it is sometimes suggested that earlier levodopa is reasonable with infusional and surgical options now available if dyskinesias become an issue.

Those favoring initial dopamine agonist treatment point out that in young patients having many years of treatment ahead of them, disabling dyskinesias should be avoided for as

long as possible if an effective alternative is available. Infusional and surgical options for the management of motor complications are only suitable for some patients and carry their own risks and side effects. It is usually possible to tailor treatment for patients based on individual social and occupational requirements.

The pragmatic approach is to introduce levodopa without undue delay when other anti-parkinsonian medications, typically dopamine agonists, at maximum tolerated doses are no longer bringing about satisfactory symptom control. An algorithm giving an overview of treatment options over the natural history of IPD is given in Fig. 5.3.



*Dopamine agonists are more likely to cause cognitive impairment and hallucinations than levodopa. Ergot derived agonists are associated with a fibrotic cardiac valvulopathy.

**Amantadine should be avoided where there is pre-existing cognitive impairment or hallucinations.

***Tolcapone is a second line COMT inhibitor after entacapone due to a rare association with hepatic failure. Liver function needs to be regularly followed while on treatment.

Fig. 5.3 Suggested treatment algorithm in idiopathic Parkinson's disease. Treatment needs to be individually tailored to each patient's age, requirement, and drug side effect profiles

Initiating Levodopa

Most treatment-naïve patients will tolerate initiation of levodopa/carbidopa at 50/12.5 mg TID. Each dose of 50/12.5 mg can then be gradually replaced by levodopa/carbidopa tablets of 100/10 mg or 100/25 mg until 100 mg of levodopa TID is reached. Many neurologists will initiate treatment using 100 mg doses of levodopa but a more cautious titration can be used in elderly patients. Nausea is the main side effect in treatment-naïve patients and can be treated with domperidone, 10 mg 30 min before or with each dose. Nausea and vomiting will usually settle within 2 weeks. For patients with persistent symptoms, the formulation with a higher dose of carbidopa should be used (Sinemet Plus, carbidopa/levodopa 100 mg/25 mg) to maximize peripheral dopa decarboxylase inhibition or this formulation can be used from the start.

There is no evidence that initiation of levodopa combined with a COMT inhibitor is of any benefit in delaying motor complications. In the early stage of levodopa therapy, before complications have developed, use of extended-release carbidopa/levodopa has no advantage over use of the standard preparation in delaying motor fluctuations. Some patients benefit from the use of dispersible levodopa in the morning to achieve faster onset of action allowing them enough freedom of movement to get dressed and washed. This approach can be useful for early morning dystonia. Dispersible levodopa can also be used on an "as required" basis for sudden "off" periods although subcutaneous apomorphine boluses can prove more practical in this situation.

Management of Advanced Parkinson's Disease

Some patients with longstanding IPD can be effectively managed on oral dopaminergics with occasional adjustments to manage the complications of chronic treatment. Others cannot achieve adequate control despite optimum oral treatment. This group experiences dyskinesias, constant swinging between "off" and "on" states, and unpredictable "offs." Options at this stage include subcutaneous apomorphine, jejunal levodopa via gastrojejunostomy (Duodopa), or stereotactic deep brain surgery (DBS). Most patients at this stage have developed additional non-motor features of IPD including cognitive impairment and mood disorders that need to be considered when choosing further strategies. Treatment with these advanced therapies usually allows reduction of total dopaminergic drug dose but almost all patients continue to require some oral medication.

Infusional Apomorphine

Continuous subcutaneous apomorphine infusion was introduced in the 1980s and is useful in advanced IPD with motor fluctuations refractory to the usual strategies. Symptoms that are not levodopa responsive will not improve. The drug is delivered via a pump connected to an infusion catheter. The needle sits subcutaneously in the abdominal wall or thigh. The rate of infusion can be adjusted with the ability to deliver bolus doses when required. Most patients require between 50 and 200 mg apomorphine per day. Some patients will take the

pump off at night but continuous infusion is possible if nocturnal symptoms are a problem. Total daily dose of levodopa can typically be halved.

The most common side effects with apomorphine are nausea, postural hypotension, daytime somnolence, and psychotoxicity. Patients need to be pretreated with domperidone for 48 h and this is continued for as long as needed afterward, usually less than 3 months. Abdominal wall nodules can form at infusion sites. Strict adherence to an aseptic technique during needle placement and regular rotation of sites can limit this problem. Ultrasound therapy and silicone gel patches can reduce the size of nodules once formed. Coombs-positive autoimmune hemolytic anemia is a rare and reversible side effect so a full blood count, reticulocyte count, and Coombs's test should be performed intermittently. Patients should be warned that apomorphine can indelibly stain clothing an olive green color.

Patients being considered for an apomorphine infusion first need to be shown to be responsive to and tolerant of an apomorphine challenge as described below. For patients already using intermittent boluses with an apomorphine pen, this is not necessary:

1. The patient is pretreated with domperidone, 20–30 mg TDS for 48 h.
2. Anti-Parkinson medications should not be taken for 4–6 h prior to the challenge. Prolonged release dopaminergics should be omitted the day before.
3. A pretreatment assessment is performed, typically including the motor subscale of the UPDRS or some other objective test of motor function (e.g., a timed walk).
4. An initial dose of 2 mg is administered. The clinical examination is repeated and the patient is observed for up to 30 min.
5. Increasing doses (in 1–2 mg increments) are given every 45 min until a 20% improvement is documented or a maximum dose of 10 mg is reached. No response at 7 mg should be considered a negative challenge.
6. The challenge is positive if a 20% improvement in pretreatment motor function is observed.

Infusional Levodopa via Jejunostomy

Delayed gastric emptying in IPD can lead to erratic and unpredictable delivery of levodopa to the small intestine. Levodopa can be administered in a gel formulation (Duodopa) by infusion through an endoscopically placed gastrostomy with a jejunostomy tube to ensure a more constant and reliable rate of delivery. This method of levodopa administration appears to have similar efficacy to subcutaneous apomorphine, reducing daily "off" time by up to 80%. The total daily dose of Duodopa required can be reduced by 20–30% with addition of a COMT inhibitor if not already being used. Patients can be treated over 16 h with a break at night or continuously over 24 h for nocturnal symptoms. This form of infusion may be useful for patients intolerant of apomorphine or those with intolerable infusion site complications. Important considerations are the need for the patient or carer to understand how to manage the pump and the relatively high frequency of complications relating to tube placement including hemorrhage, peritonitis and the possibility that tubes can kink, become displaced, and require replacement.

Surgical Procedures

Prior to the development of levodopa, a number of surgical techniques were attempted to treat the motor symptoms of IPD. Thalamotomy emerged as the most effective, particularly for tremor. Surgical options faded from prominence with the miracle of levodopa; however, the prevalence of motor complications after long-term levodopa exposure has renewed interest. DBS has replaced ablative procedures as the technique of choice, as it does not destroy brain tissue, it is potentially reversible, and adjustments can be made postoperatively. The gait, speech, swallow, and cognitive disturbances that are associated with bilateral ablative procedures are also less of a concern as stimulation can be reduced or aborted if required.

DBS does not offer superior control of the cardinal symptoms of IPD compared to levodopa. Its role is in the management of motor complications and the management of treatment-refractory tremor. Levodopa-responsive patients with dyskinesias or motor fluctuations affecting their quality of life are the best candidates.

The best results from DBS are seen with younger patients. The presence of cognitive impairment is a relative contraindication as cognition can worsen with any surgical penetration of the brain. However, recent prospectively gathered data from patients undergoing stimulation of the subthalamic nucleus is reassuring. Other adverse effects from DBS include hemorrhage, infection, speech impairment, dystonia, and wire breakage. Even in young patients, there can be impaired cognition, depression with suicide attempts, and an incomplete response. Postoperative follow-up programming of the stimulators is an ongoing process.

Targets for ablative and DBS procedures are discussed below:

- *Thalamotomy and thalamic stimulation*: The target is the ventral intermediate nucleus and best effects are seen for contralateral intractable tremor that can be relieved in at least 70% of cases. The effect on other parkinsonian features is less impressive. Although a unilateral lesion carries a small risk, bilateral operations result in dysarthria in 15–20% of patients. Thalamic stimulation seems to be safer than ablation and can be equally effective against tremor.
- *Pallidotomy* and *pallidal stimulation*: The effects of globus pallidus stimulation are broadly similar to pallidotomy. The target is the posterolateral part of the globus pallidus interna (GPi) and outcomes are best treating contralateral dyskinesia with less benefit for bradykinesia and tremor. The target in the GPi is believed to be the site of afferent excitatory glutamatergic fibers coming from the subthalamic nucleus, which is overactive in IPD.
- *Subthalamotomy and subthalamic nucleus* (*STN*) *stimulation*: The beneficial effect of targeting this nucleus fits well with observed STN overactivity in IPD. The STN has a central role in the classic model of basal ganglia function, providing excitatory input to the GPi. Subthalamotomy has been infrequently performed in IPD because of the potentially serious side effect of producing contralateral hemiballism. This risk is not present with DBS, which is now the most commonly performed procedure in the treatment of bradykinesia, rigidity, and tremor. The antiparkinsonian effect is no better than the best levodopa effect (except for tremor where surgery seems to be superior).

Management of Acute Deterioration in Parkinson's Disease

Sustained functional deterioration in IPD should be investigated thoroughly for a reversible cause. Like many chronic neurological conditions, any systemic illness can cause an acute deterioration from baseline. If treatable, a return to baseline should be expected but this can take weeks after the original insult has resolved. Two causes of acute deterioration worth highlighting are missed medications and inappropriate exposure to dopamine antagonists. Both problems can occur when patients are admitted for surgery, either as an emergency or electively. Involvement of a neurology team in these cases is useful, particularly for patients who are fasting or with advanced disease. Causes of acute deterioration to consider in IPD and their management are given below. In general, an increase in levodopa dose in the setting of one of these precipitants is preferably avoided.

- *Sepsis*: Perform a full septic screen and treat appropriately with advice from microbiology if required.
- *Dehydration*: Rehydrate and correct any electrolyte disturbances.
- *Constipation*: Treat with laxatives and confirm resolution on plain film of abdomen. The aim should be to have at least one normal or soft bowel motion daily.
- *Stress or anxiety*: Treat appropriately with psychiatry advice if required.
- *Missed medication or inappropriate sudden withdrawal of medication*: Reinstate at previous effective dose.
- *Exposure to dopamine antagonists* (*e.g., prochlorperazine*): Discontinue drug, use an acceptable alternative.
- *Concurrent, medical, or surgical illness*: Supportive care, physiotherapy to maintain mobility and expect slow return to baseline level.
- *Hardware or battery failure if deep brain stimulator in situ*: Immediate neurosurgical referral.
- *Cervical spine injury*: Consider if after a fall there is a deterioration in gait with pyramidal signs in the lower limbs or a history of cervical spondylosis. Compromise of the cervical spine should also be considered in patients with deteriorating mobility despite increasing amounts of levodopa, particularly when resulting dyskinesias are limited to the head and neck region.
- *Serotonin syndrome*: Consider if there has been a recent introduction of an SSRI or TCA; stop any potential causative agent and support acutely.
- *Depression*: Common in PD and may present with somatic symptoms resembling hypophonia and bradyphrenia. Consider an SSRI or tricyclic antidepressant.

Long-Term Complications of Treatment

Motor Fluctuations

The pharmacokinetics of levodopa show a peak plasma concentration in about 30 min, and an elimination phase of about 90 min. Despite this, patients typically report no variability in their symptoms initially despite a TID dosing regime. This long-duration benefit may be

due to the buffering effect of dopamine storage in surviving nigral nerve terminals and to a long-lasting postsynaptic effect, facilitating this early "honeymoon period." Ongoing neuronal loss accompanied by functional receptor changes in the striatum may be important in the genesis of motor complications. Over time, the clinical response becomes shorter, unpredictable, and often inadequate. The long-duration benefit is lost and only the short-duration benefit is seen.

Motor fluctuations typically begin with an end-of-dose deterioration or *wearing off*, defined as a return of parkinsonian symptoms less than 4 h after the last dose. Patients gradually become aware of increasing contrast between "on" and "off" time. Initially, "off" time will be prior to a scheduled levodopa dose, but unpredictable "offs" unrelated to the timing of medications may evolve. Patients sometimes report a "not on" (dose failures) or "delayed on" phenomenon where they get no response or a delayed response to a particular dose. Most dose failures are due to delay in levodopa entering the duodenum where it can be absorbed. Having the patient crush the tablet between his teeth and swallowing with ample amount of water could dissolve levodopa faster and facilitate its entry into the small intestine. Motor "offs" can be accompanied by non-motor "offs" with patients reporting anxiety, autonomic symptoms, dysphoria, and pain during these periods. Non-motor "off's" do not always coincide with motor fluctuations and may be difficult to recognize. Patients with non-motor "offs" tend to take more frequent dosings of levodopa in an effort to avoid these intolerable "offs."

Treatment adjustment aiming for continuous dopaminergic stimulation remains a mainstay of treating motor fluctuations. Changes in dosing schedules and the addition of drugs that prolong the life of dopamine at the dopamine receptor can assist in "smoothing out" the levodopa response. Strategies that are commonly used are given in Table 5.7.

Dyskinesias

These are frequently mild choreic movements that are often unnoticed by the patient and managed with small reductions in levodopa if bothersome. In some cases, dyskinesias are disabling and severe, consisting of chorea, ballism, dystonia, or a combination of these. Dyskinesias are more common in young-onset patients, of whom 70% are affected after 3 years of treatment. Initially, patients will spend only a small part of the day in either the "off" or dyskinetic state with the "on" period in between representing the target "therapeutic window" where function is adequate. Over time, this window shrinks in duration with patients flipping from the "off" state to being dyskinetic. Patients at this stage will often prefer to be dyskinetic as it is only when dyskinetic that they can have some freedom of movement. Distressed relatives may not appreciate this functional significance of dyskinesias. Dyskinesias can be subdivided into: 1) peak-dose dyskinesias, appearing at the height of antiparkinsonian benefit, 20 min to 2 h after a dose, 2) diphasic dyskinesias, usually affecting the legs, appearing at the beginning and end of the dosing cycle, and 3) "off" dystonia, which can be painful, sustained cramping, appear during "off" states and may be seen as early morning dystonia presenting as foot cramps. Judicious introduction of levodopa with or without dopamine agonists can delay the onset and reduce the severity of dyskinesias, although over time they are inevitable, particularly in younger patients. Treatment strategies are outlined in Table 5.8.

Table 5.7 Management of motor fluctuations in Parkinson's disease

- Levodopa should be taken 1 h before or an hour after eating to enhance passage from stomach to small intestine and to reduce competition against amino acids for large neutral amino acid transporters in the small intestine. This can improve the "delayed on" or "no-on" phenomena.
- Constipation is almost universal in PD. Regular bowel habit can contribute to an overall strategy to make levodopa absorption and motor response more predictable.
- Additional doses reduce the inter-dose interval and can resolve wearing off. Patients with advanced IPD will commonly require levodopa every 3 hours throughout the day.
- Addition of dopamine agonists, which have longer half-lives, particularly modified release formulations of ropinirole, pramipexole, or the rotigotine patch, reduce both the frequency and the depth of the "off" states.
- Addition of selegiline, rasagiline, or COMT inhibitors (entacapone or tolcapone) can improve mild wearing-off. The addition of COMT inhibitors may require a reduction in levodopa dose of 15–30% as peak-dose dyskinesias can be precipitated, or worsen.
- Slow-release forms of carbidopa/levodopa (Sinemet CR) have been used to improve wearing off, although plasma levodopa levels can be erratic and response unpredictable
- Patients who have rapid transitions between "on" and "off" can benefit from dispersible forms of levodopa (Madopar Dispersible). This speeds up the transit of levodopa to the small intestine giving them a "kick-start." Prefilled apomorphine pen devices delivering bolus doses subcutaneously can also be used for a similar effect.
- Infusional therapies aim to achieve continuous dopaminergic stimulation to smooth out motor fluctuations. Levodopa in a gel is infused directly into the small intestine (Duodopa), avoiding erratic passage through the stomach. Subcutaneous apomorphine bypasses the gut to provide continuous symptomatic relief although patient selection is important.

Table 5.8 Strategies for the management of dyskinesias in Parkinson's disease

1. Peak-dose dyskinesias can be improved by small reductions in each levodopa dose, facilitated by the addition of a dopamine agonist. COMT and MAO-B inhibitors can be added to facilitate weaning of levodopa that might lead to wearing off; alternatively, the inter-dose interval can be reduced.
2. Avoid long-acting formulations of levodopa that can accumulate over the course of the day, leading to dyskinesias that can be prolonged.
3. Amantadine can reduce the severity of dyskinesias, but a dose of at least 400 mg/day is usually required and any benefit may not persist. Cognitive impairment, nightmares, hallucinations, and myoclonus are not uncommon side effects and limit its use in older patients.
4. Diphasic dyskinesias are more difficult to treat. Increasing the dosage of levodopa can be effective but peak-dose dyskinesia usually ensues. A switch to a dopamine agonist is more effective; low doses of levodopa are used as an adjunctive agent.
5. The principle of treating "off dystonia" is to try to keep the patient "on" most of the time. Here again, using a dopamine agonist as the major antiparkinsonian drug, with low doses of levodopa as an adjunct, can often be effective.
6. If adjustment of oral medications is ineffective, infusional (subcutaneous or jejunal) or surgical options should be explored with good results in appropriately selected patients.

Freezing

Freezing, a sudden inability to move lasting seconds to minutes, can be seen at any stage of PD but typically is seen with motor fluctuations in advanced disease. If early in the illness, think of atypical parkinsonism such as PSP or vascular parkinsonism. Any movement can be involved, but freezing of gait is the most disabling form and can be an important cause of falls where upper body momentum causes loss of balance on freezing when walking or turning. "Off-freezing" must be distinguished from "on-freezing." Off-freezing was described before the advent of levodopa therapy and therefore is a disease phenomenon and not a complication of treatment; it responds to levodopa. On-freezing remains an enigma; patients can be seen to freeze despite good control of all other symptoms. The etiology is unknown but non-dopaminergic systems are probably involved.

Although rarely successful, reduction of the total amount of "off" time by increasing dopaminergic medications is the best approach to treating "off-freezing." There is no proven treatment for "on-freezing" but reduction of total levodopa dose can sometimes help, but this can worsen all other levodopa-responsive symptoms. Both on- and off-freezing seem to correlate with both the duration of illness and the duration of levodopa therapy. Early use of the MAO-B inhibitors rasagiline and selegiline may reduce the risk of developing the freezing phenomenon. Non-pharmacological approaches include walking aids to reduce the risk of falling. The use of sensory cues takes advantage of *kinesie paradoxale* whereby the inclusion of a sensory stimulus into the motor routine appears to activate a more effective motor program. Examples include the use of a metronome, a bar on a walking cane to step over, or internally generated cues such as counting or attempting to walk like a soldier.

New targets for DBS aim to target those motor symptoms not responsive to levodopa, in particular freezing and postural instability. Initial unblinded studies of surgery targeting the pedunculopontine nucleus suggested that stimulation of this mainly cholinergic nucleus might be of benefit in freezing of gait, but this has not been borne out in blinded studies.

Neuropsychiatric

Confusion, agitation, hallucinations, delusions, paranoia, and mania are probably related to activation of dopamine receptors in non-striatal regions although psychosis can be a primary disease phenomenon, especially if the patient has developed dementia. Dopamine agonists more often bring out these complications, particularly at high doses. Early hallucinations or psychosis should prompt the question of underlying Lewy body dementia or concomitant Alzheimer disease. Where possible, reversible causes of any deterioration should be sought before this assumption is made:

1. Eliminate sepsis, dehydration, and electrolyte imbalances as a cause of a delirium.
2. Addition of an atypical neuroleptic, preferred for their affinity for D4 more than D2 receptors, such as quetiapine and clozapine.
3. Discontinue any drugs that may be responsible, typically in the following order based on propensity to cause neuropsychiatric side effects – anticholinergics, amantadine, MAO-B inhibitors, and dopamine agonists.
4. If discontinuation of the above is ineffective, patients on a high dose of levodopa should have their dose reduced down to the minimal effective dose.

Neuroleptic drugs can induce drowsiness and should therefore be given at bedtime. Start with a dose of 12.5 mg of quetiapine to avoid the biweekly blood counts required with clozapine although it is less effective (see above). If clozapine is not tolerated, other drugs, including small doses of olanzapine, molindone, aripiprazole, or pimozide can be used. If the parkinsonism deteriorates, lowering the dosage of levodopa to avoid the psychosis is preferable to maintaining a high dose of the antipsychotic. Levodopa should not be discontinued suddenly; abrupt cessation may induce a neuroleptic malignant-like syndrome, sometimes referred to as parkinsonism–hyperpyrexia syndrome.

Impulse Control Disorders

Impulse control disorders (ICDs) are seen in the general population, but are more common in IPD. ICDs represent an inability to resist a drive or temptation to perform an act harmful to others or oneself. Pathological gambling is most often encountered, but hypersexuality, excessive shopping, reckless generosity, and hyperphagia are also described. Significant financial, personal, and social harm can be done. Young male patients with early onset disease are at particular risk.

ICDs appear to be specific to treatment with dopamine agonists with a dose-response effect. This may be due to their affinity for D3 receptors of the mesocorticolimbic pathways, stimulation of which is integral to reward and reinforcement behavior. *Dopa dysregulation syndrome* (DDS) is a related phenomenon whereby a patient will take excessive and repeated doses of levodopa or a fast-acting agonist such as apomorphine, often despite disabling dyskinesias. Soluble forms of dopamine are often preferred due to their rapid onset of action. *Punding* is repetitive behavior involving purposeless motor tasks such as picking at oneself, taking apart watches and radios, or sorting and rearranging of common objects, such as lining up pebbles, rocks, or other small objects.

The management of ICDs involves early recognition and reduction of dopamine agonist doses to a minimum or stopping completely. This approach is effective in the majority of cases. Change to an alternative agonist is of little value, and in some cases, levodopa will have to be increased to compensate for loss of the agonist. Patients with dopa dysregulation syndrome need to have their levodopa dose reduced to see an improvement. Fast-acting, water-soluble forms should be avoided completely. A difficult aspect of managing ICD and DDS is obtaining the history from the patient or family due to embarrassment. Specifically asking for behavioral changes in the spectrum of ICD is therefore vital.

Recent and Future Developments

New Agonists, Continuous Dopaminergic Stimulation

Continuous dopaminergic stimulation remains a target to achieve sustained control over symptoms without the complications associated with prolonged treatment. A number of treatment options are now available, which blunt the peaks and troughs of pulsatile stimulation, including direct infusion of levodopa into the small intestine (Duodopa) and

transdermal delivery of rotigotine. Some dopamine agonists are now available in a once-daily formulation that may further smooth the response to treatment. New dopamine agonists and delivery methods in the future will need to be potent enough to remain effective without the addition of levodopa since it appears that initial agonist treatment does not prolong the latent period before the onset of levodopa-induced dyskinesias.

Dopaminergic Cell Transplantation

To date, no double-blind controlled trial has shown a benefit of dopaminergic cell transplantation in IPD. Individual case series have been promising with postmortem and radiological (^{18}flourodopa PET) evidence of functioning graft tissue with some patients enjoying significant and even complete withdrawal of oral therapies. An important adverse effect noted in over 50% of transplanted patients in one study is so-called "off medication dyskinesias." This form of dyskinesia can be persistent, lasting for days or weeks. It is also possible that in time transplanted neurons will be susceptible to the same degenerative process that affected native neurons in the first place. More research is required to determine what immunosuppressive regime, quantity of transplanted cells, and target patient group are required to improve outcomes. Importantly, even if eventually successful, dopaminergic cell transplantation may not benefit the disabling non-dopaminergic symptoms of IPD.

Stem Cell Implantation

Stem cell-based therapies are an attractive option given the potential of these cells to repair degenerating or injured neural circuits and the ability to generate cell lines in vitro. Stem cells can be derived from preimplantation human blastocysts. Neural progenitor cells are alternative sources of implantable cell lines, derived from embryonic tissue or postoperative adult specimens. Induced pluripotent stem cells are generated from skin fibroblasts through genetic manipulation and are an exciting proposition in that they avoid the ethical dilemma of using fetal tissue, they are in abundant supply, and do not necessitate immunosuppression.

No trials to date have evaluated the effect of stem cells in human patients, but animal studies are ongoing. Before a human trial can take place, the safety profile of implanting stem cells needs to be further evaluated. A major concern has been the development of malignant tumors following the implantation of undifferentiated stem cells in animal studies and in one reported human case involving a young boy with ataxia telangiectasia, who developed a multifocal glioma derived from transplanted stem cells. Furthermore, the ethical issues surrounding stem cell-based therapies need to be resolved individually in every jurisdiction. Like dopaminergic cell transplantation, even if successful, stem cell implantation is unlikely to address the many non-motor features of IPD.

Management of Non-dopaminergic Symptoms

Much of the Parkinson's disease research literature has been devoted to the management of the complications of long-term levodopa treatment. Infusional dopaminergic treatments and

functional neurosurgery have reached a point where motor fluctuations can be addressed to some satisfaction, although more options are needed for patients not suited to current treatment modalities. Attention will increasingly turn to the non-dopaminergic symptoms experienced in advanced PD, in particular dementia, freezing, and postural instability. Cholinesterase inhibitors offer limited benefit in the management of dementia in the context of PD. Their general role in mild cognitive impairment is uncertain and many patients with cognitive impairment in PD will only have subtle frontal–dysexecutive features. Safinamide targets dopaminergic and glutaminergic targets and may have neuroprotective properties and a role in cognitive impairment, although clinical trials are required.

Gene Therapy

Gene therapy has the potential to restore striatal dopaminergic function to a more physiological level by delivering proteins such as aromatic acid decarboxylase (AADC), 3,4-dihydroxyphenylalanine (DOPA), and glutamic acid decarboxylase (GAD) via an adeno-associated viral vector. Alternatively, genes coding for trophic factors delivered to the basal ganglia might preserve or prolong survival of remaining dopaminergic neurons.

Neuroprotection

Because the exact etiology of IPD is unknown, it remains difficult to know where the development of a neuroprotective agent should be targeted. A number of potential targets have emerged, most notably mitochondrial dysfunction from the study of inherited forms of the disease. Other possibilities include abnormalities in apoptotic pathways, excitotoxicity, and oxidative stress. A combination of factors may be at play with a cumulative effect to produce the parkinsonian "phenotype." Identification of genes, which are risk factors for the development of IPD from genome-wide association studies, may be informative in the design of neuroprotective regimes to target these potential risk factors individually. As stated previously, by the time patients present for treatment, the majority of nigrostriatal dopaminergic neurons have been lost. If a disease-modifying agent is found it will need to be introduced as early as possible. To enable this, a reliable biomarker of underlying susceptibility to PD in asymptomatic, at-risk individuals needs to be identified.

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