Section 1 General aspects

Chapter 1

Overview of Parkinson's disease: epidemiology, diagnosis, course, medical and surgical management

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Introduction

This chapter introduces Parkinson's disease (PD) as a neurodegenerative disorder that has both motor and non-motor components. Given that the rest of the chapters will focus on cognitive and behavioral issues related to Parkinson's disease and its treatment, this discussion focuses on the epidemiology, current views on etiology and pathogenesis, and the management options used to treat the primary disease. Laboratory scientists and clinicians, including neurologists, psychiatrists, and neurosurgeons, as well as psychologists, nurses, social workers, and other professionals, can use the information in this chapter as a foundation for an appreciation of the specific issues related to the cognitive and behavioral challenges faced by Parkinson's disease patients and their families.

Epidemiology

PD is the second most common neurodegenerative disorder. The incidence is similar worldwide, and is estimated at 13–23.8 per 100 000 with a peak incidence between 75 and 84 years of age [1,2]. The prevalence increases with age, with more than 1% affected over the age of 65 years, increasing to more than 4% of the population in those over the age of 85 [3]. The reported prevalence of PD is 107–187 per 100 000 population in North American studies [1,2]. PD affects both sexes, with a slight male predominance. Whether racial factors contribute significantly to geographic variation remains to be clarified; however, the lowest reported rates are in those of Asian and African descent [2]. The prevalence of PD within races is not uniform across different environmental conditions.

Etiology and pathogenesis

The etiology of PD is thought to represent a convergence of aging, genetic susceptibility, and environmental exposures, with each case being due to a unique combination of these contributors. Sporadic cases likely result from a complex interaction of these factors, with advancing age being the main risk factor. Pure monogenic causes represent approximately 10% of PD cases [4]. First-degree relatives of sporadic PD patients are 2–3 times more likely than relatives of controls to have PD, suggesting genetic contributions even in forms of PD otherwise termed sporadic [5]. Environmental exposures may be beneficial or deleterious. The most extreme examples are patients exposed to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [6]. There have been reports of increased risk in those who have had exposure to insecticide or well water as well as rural residency in industrialized agricultural societies at the time of diagnosis. Other exposures, including smoking, caffeine consumption, higher uric acid, and anti-inflammatory drug use, may provide environmentally related protective effects against PD [7].

The loss of dopaminergic neurons in the substantia nigra results in the cardinal motor manifestations of PD. The molecular events that lead to this degeneration have not been fully elucidated. α-Synuclein has been hypothesized to play a causative role, not only because of its effect on dopamine synthesis but also because of its role in synaptic vesicle fusion. In

Neuropsychiatric and Cognitive Changes in Parkinson's Disease and Related Movement Disorders, ed. Dag Aarsland, Jeffrey Cummings, Daniel Weintraub, and K. Ray Chaudhuri. Published by Cambridge University Press.

vitro, α-synuclein regulates the production of dopamine by interacting with the production of tyrosine hydroxylase (TH), the rate-limiting enzyme in dopamine synthesis [8]. Compelling evidence suggests a role for α-synuclein in vesicular fusion. In transgenic mice, overexpression of α-synuclein results in impaired synaptic vesicle exocytosis in hippocampal neurons [9]. These results, although yet to be replicated in vivo, associate the high α-synuclein expression seen in PD with the marked defect in synaptic transmission and neurotransmitter release that typifies PD [10]. The preferential vulnerability that is seen with dopamine neurons in the substantia nigra is likely the result of failure of normal cellular physiology [8].

Several hypotheses as to the pathogenesis of PD have been suggested, including protein misfolding and aggregation, mitochondrial dysfunction, oxidative stress, and inflammation. An abnormality of protein misfolding and aggregation was suggested by the consistent identification of α-synuclein as a component of Lewy body inclusions, the neuropathologic hallmark of PD. This observation sparked the hypothesis that dysfunction of the ubiquitin–proteasome system (UPS) may play a causative role in PD. Ubiquitin functions to tag proteins that must be eliminated from cells through proteasomal degradation. Inactivation of the UPS could lead to an accumulation of ubiquitylated proteins with aggregation into inclusion bodies and resultant neuronal death. The hypothesis of UPS dysfunction predisposing an individual to PD was further supported by the discovery of parkin (*PARK2*), one of the causal genes in autosomal recessive PD; this gene encodes a ubiquitin ligase (E3) enzyme, which has a role in transferring activated ubiquitin to a specific substrate protein during ubiquitination. Parkin also regulates the elimination of damaged mitochondria by autophagy, a function also regulated by *PINK1*. This further supported the association of ubiquitylation with the autophagy system [11,12]. The UPS and the autophagy–lysosome pathway (ALP) are the two main systems involved in protein degradation in eukaryotic cells. These two degradation pathways are interrelated, with ubiquitin functioning in both systems. Chaperone-mediated autophagy (CMA), the only autophagic pathway that allows for selective degradation of soluble proteins in lysosomes, is thought to be decreased in PD [12,13]. Chaperones are important both for folding of functional and degradation of dysfunctional proteins. Additionally, they may assist the protein targeting to the lysosome for degradation by the CMA pathway, and chaperones can also help sequester toxic proteins into inclusion bodies. Chaperone failure could compromise the ability of cells to adapt to stress conditions, leading to protein misfolding, inclusion body formation, and subsequent neurodegeneration [13].

Mitochondrial dysfunction, oxidative stress, and inflammation have also been suggested to play a fundamental role in PD. The role of mitochondrial dysfunction is supported by several findings, including complex I deficiency in the substantia nigra, mitochondrial abnormalities both in the brain (confined to the nigra) and in other cells, and specific gene mutations that induce dopaminergic cell death resulting in familial forms of PD. Oxidative stress is also considered an important factor in the pathogenesis of PD. Although the exact origin of the reactive oxygen species (ROS) involved has yet to be elucidated, the process appears to be a more generalized one, not only involving the brain [12]. There has been a growing body of research suggesting a role for neuroinflammation in the pathogenesis of PD. Markers of inflammation, including microglia, cytokines, and inflammation-related enzymes, have been reported to be increased in the substantia nigra and cerebral spinal fluid of PD patients. These factors have been shown to cause cell death by activating the cell death pathway, or indirectly by production of ROS which converge on mitochondrial dysfunction and activation of intrinsic cell death pathways [14]. Anti-inflammatory drugs have therefore been of interest as a potential agent to protect against cellular stress and degeneration (see below).

Genetics of PD

The α-synuclein gene, *SNCA*, has classically been described in familial cases of PD. In sporadic PD, a strong association between a common single nucleotide polymorphism and PD has been demonstrable, suggesting an increased susceptibility. The suggested disease mechanisms include altered control of transcription, regulation of alternative splicing, or altered stability of mRNA through post-transcriptional processing. Although elevation of α-synuclein expression is thought to be causative in familial cases, the role in sporadic cases remains unclear [8].

Historically, PD was considered to be a sporadic degenerative disease. More recently, genome-wide

association studies (GWAS) have brought to light a genetic link. A recent review highlighted the clinical characteristics of each monogenic form of PD as well as risk variants for PD confirmed with GWAS.

Genes associated with autosomal dominant forms of PD include *SNCA* at the PARK1/PARK4 locus on the long arm of chromosome 4 as well as *LRRK2* at the PARK8 locus on chromosome 12. Multiplications and three missense mutations (A53T, A30P, and E46K) in *SNCA* have been reported to cause PD. *SNCA* duplications lead to late-onset levodopa-responsive parkinsonism, whereas triplications cause earlier disease onset with rapid progression and prominent dementia. A53T mutations result in an early-onset severe form of parkinsonism with rapid progression and prominent dementia, while A30P mutations result in late-onset parkinsonism with mild dementia. The precise mechanism of toxicity is still not well understood, but it has been suggested that these mutations, which alter the amino acid composition, may lead to an increased tendency for oligomer and fibrillary aggregate formation leading to neuronal dysfunction and cell death. In comparison, individuals with PARK8-linked PD display clinical characteristics similar to those in sporadic PD; dementia is not a common feature. Although the inheritance pattern is autosomal dominant, there is incomplete penetrance observed [15].

Genes associated with autosomal recessive PD include *parkin* at the PARK2 locus, *DJ-1* at PARK7, *PINK1* at PARK6, and *ATP13A2* at PARK9. Parkin is mapped to the long arm of chromosome 6. This form of PD has a young disease onset. Limb dystonia (legs) as well as a diurnal fluctuation are classically described, and the progression of parkinsonism is typically slow with good responsiveness to levodopa. *DJ-1* and *PINK1* mutations both cause early-onset disease with slow progression and levodopa responsiveness. At chromosome 1p36, mutations at *ATP13A2* present clinically at an early age and display levodopa-responsive parkinsonism, pyramidal signs, dementia, and supranuclear gaze palsy. PARK14- and PARK15-linked parkinsonism have also been described among the autosomal recessive causes, but the exact pathogenesis is not well known [15].

In addition to the aforementioned genes, loss-of-function mutations in the glucocerebrosidase gene (causative gene in Gaucher disease) increase the risk for PD. Several other common variants in *MAPT*, *LRRK2*, *SNCA*, and *HLA-DRA* are considered risk factors for PD [15].

Neuropathology

The pathologic hallmark of PD is dopaminergic cell loss within the substantia nigra pars compacta. Lewy bodies, spherical eosinophilic cytoplasmic aggregates, are present in affected regions of the brain. They contain various proteins, predominantly α-synuclein, as well as parkin, ubiquitin, and neurofilaments [16]. Historically, the definitive diagnosis has depended on the presence of these two neuropathologic features at autopsy. However, this has been called into question more recently due to reports of some familial cases, linked to parkin, which may lack Lewy bodies. Classically, motor dysfunction is thought to become clinically apparent when at least 80% of striatal dopamine and 50% of nigral neurons are lost [17]. Early on in the disease course Lewy body pathology is present in the lower brainstem, olfactory bulb, and autonomic nervous system with relative sparing of the substantia nigra. Braak *et al.* described the neuropathological changes that are seen in the brain during the disease progression, identifying six stages [18]. In stages 1 and 2, pathologic changes are seen in the medulla oblongata and pontine tegmentum. This represents the clinically presymptomatic stages. Symptomatic parkinsonism becomes apparent in stages 3 and 4 when the substantia nigra as well as other nuclei within the midbrain and forebrain become involved. Late stages of the disease, 5 and 6, represent neocortical involvement. This anatomically ascending pattern of neurodegeneration has been debated extensively, and is not likely to be fully sound, but it has served as a model for studying the evolving problems encountered in PD and for the elucidation of a preclinical phase, which is the focus of considerable current research.

Clinical course

Prodromal phase

Whereas the motor hallmarks of PD are tremor, bradykinesia, rigidity, and gait/balance problems, current views suggest that non-motor elements may precede these signs and be the first manifestations of PD (Table 1.1). Prospective data suggest that olfactory problems, rapid eye movement (REM) behavior disorder (RBD), constipation, and depression may predate the motor phase [19]. These problems are thought to reflect Lewy body involvement in the lower brainstem, olfactory bulb, and spinal cord [20].

Table 1.1 Clinical features of PD.

Motor (cardinal features)	Non-motor
Rest tremor	Sensory Olfactory dysfunction Paresthesias, dysesthesias Temperature, pain
Bradykinesia	Autonomic Constipation Orthostatic hypotension Urogenital dysfunction
Rigidity	Neuropsychiatric Cognitive impairment/dementia Depression/apathy/anxiety Hallucinations/psychosis Sleep disturbances
Postural instability	

This premotor or prodromal phase likely occurs at a time when 50% or greater loss of dopaminergic cells in the substantia nigra has already occurred [17]. Epidemiologic studies of non-motor manifestations suggest that this preclinical phase may begin even 20 years before the motor manifestation of PD [21]. These non-motor symptoms are prevalent not only in the preclinical phase but throughout the disease course, with a significant correlation between number of symptoms and severity/duration of disease [22]. As such, the focus of neuroprotective studies has been to seek out patients in this prodromal phase to better understand the impact on progression of disease. Although this concept is appealing, a specific biomarker of PD that can diagnose the disease before the motor manifestations appear is yet to be established.

Diagnostic phase: motor symptoms

When PD is first apparent motorically, rest tremor, bradykinesia, and rigidity are usually found on both sides of the body but with one side more involved than the other. The rest tremor is 4–6 Hz, classically described as "pill rolling" in the hand. Tremor may also be present in the lower extremity, jaw, tongue, and very rarely the head. With voluntary movement, the tremor is initially suppressed but may recur after several seconds (overflow tremor). Bradykinesia causes slow and deliberate movement without weakness, and is usually assessed with rapid finger tapping or other simple tasks in the office. Bradykinesia affects activities of daily living such as buttoning, handwriting, and rising from a chair. Rigidity is an increase in muscle tone to passive movement and is detected by the physician, who will detect the typical "cogwheeling" of increased tone in both agonist and antagonist muscles. Gait is impaired with small shuffling steps, difficulty pivoting as the patient changes direction, and decreased arm swing. In more advanced disease, frequent arrests of movement or "freezing" can be seen. Postural instability is the fourth cardinal feature of PD, but does not occur early in the disease. When postural instability develops, stumbling, falling, and a propulsive or retropulsive gait typically occur. Falls then become a prominent risk because of the danger of hip fractures and immobility. The Unified Parkinson's Disease Rating Scale (UPDRS) has been the most widely used clinical rating scale for PD. In 2001 the Movement Disorder Society (MDS) sponsored a critical appraisal of the scale and developed a revised, expanded scale (MDS-UPDRS) which consists of four parts: non-motor experiences of daily living, motor experiences of daily living, motor examination, and motor complications (Table 1.2) [23].

Non-motor symptoms appearing in the context of motor signs of PD

Whereas the appearance of non-motor features preceding the onset of motor symptoms in PD is still incompletely defined, several non-motor symptoms develop in the context of well-established motor problems. These signs become more prominent as the disease progresses and account for the major sources of disability in late disease [24]. Neuropsychiatric and cognitive dysfunction is the primary focus of this textbook, so this will be discussed in other chapters. Features otherwise not discussed in subsequent chapters are highlighted briefly here.

Sensory symptoms and pain may be prominent early in the disease course. Olfactory dysfunction has been reported in up to 90% of PD patients, and is associated with degeneration of olfactory bulb and anterior olfactory nucleus [25]. Other sensory symptoms include numbness, tingling, burning, aching, coldness, heat, and pain. The pathophysiology of pain in PD is multifactorial and may be due to

Table 1.2 MDS-UPDRS rating scale for PD (Goetz *et al.* 2008 [23]).

Part I: Non-motor experiences of daily living[a]

- Cognitive impairment
- Hallucinations and psychosis
- Depressed mood
- Anxious mood
- Apathy
- Features of dopamine dysregulation syndrome
- Night-time sleep problems
- Daytime sleepiness
- Pain and other sensations
- Urinary problems
- Constipation problems
- Lightheadedness on standing
- Fatigue

Part II: Motor experiences of daily living[a]

- Speech
- Salivation and drooling
- Chewing and swallowing
- Eating tasks
- Dressing
- Hygiene
- Handwriting
- Doing hobbies and other activities
- Turning in bed
- Tremor
- Getting out of bed, car, or deep chair
- Walking and balance
- Freezing

Part III: Motor examination[a]

- Speech
- Facial expression
- Rigidity of neck and four extremities[b]
- Finger taps[b]
- Hand movements[b]
- Pronation/supination[b]
- Toe tapping[b]
- Leg agility[b]
- Arising from chair
- Gait
- Freezing of gait
- Postural stability
- Posture
- Global spontaneity of movement
- Postural tremor of hands[b]
- Kinetic tremor of hands[b]
- Rest tremor amplitude[b]
- Constancy of rest tremor

Part IV: Motor complications[a]

- Time spent with dyskinesia
- Functional impact of dyskinesias
- Time spent in the "off" state
- Functional impact of fluctuations
- Complexity of motor fluctuations
- Painful "off" state dystonia

[a] Each item has five responses: 0, normal; 1, slight; 2, mild; 3, moderate; 4, severe.
[b] Items assessed by both right and left measurements.

musculoskeletal causes and arthritis, to compressive neuropathies from bradykinesia or dyskinesia, and to dystonia that is part of PD or its treatment.

Dysautonomia in PD includes constipation, orthostatic hypotension, and urogenital dysfunction. Constipation has been reported to predate the extrapyramidal signs of PD. Abbott *et al.* assessed bowel movement frequency in elderly men enrolled in the Honolulu–Asia Aging Study. After adjusting for possible confounding variables such as tobacco and alcohol use as well as cognitive function, they concluded that infrequent bowel movements were associated with incidental Lewy body deposition on postmortem examination in those without clinical PD or dementia [26]. The earliest affected brain regions according to Braak staging are in the parasympathetic nuclei in the lower brainstem, which provide preganglionic parasympathetic innervation to the ganglia in the visceral organs. Additionally, intramural parasympathetic ganglia in the gastrointestinal tract have been shown to be vulnerable to α-synuclein pathology [27]. This is associated with a high intestinal tract time, thus leading to constipation. Orthostatic hypotension and urogenital dysfunction are thought to be more apparent in the later stages of the disease. Degeneration of cardiac sympathetic nerves is thought to begin in the early disease process of PD and increases with disease duration and severity [28]. When considering orthostatic hypotension in PD, one must determine whether the etiology is primary or due to medication. Urogenital dysfunction in PD encompasses urinary frequency and urgency, incomplete bladder emptying, double micturition, urge incontinence, and erectile and ejaculatory failure. Urinary dysfunction is thought to involve detrusor overactivity due to decreased basal ganglia output, which overall has an inhibitory effect on the micturition

reflex in healthy individuals [29]. Male erectile dysfunction is common and can have very important effects on self-image and quality of life; it particularly becomes problematic in men who also are afflicted by impulse control disorders (see later chapters) or other psychiatric complications.

These non-motor symptoms have been reported to have a greater impact on health-related quality of life than motor symptoms, and thus become the increasing focus of recognition and management during chronic health care of PD patients [30].

Differential diagnosis and diagnostic evaluation

The other diagnoses to consider include other causes of parkinsonism and other disorders that can cause tremor, poor coordination, or falling. In the first category, atypical parkinsonism (progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration, juvenile Huntington's disease, among others) is to be considered if additional neurological signs are detected or if the temporal pattern is not typical for PD. Drug-induced parkinsonism (antipsychotics, metoclopramide, reserpine, and any agent that blocks dopamine receptors or depletes central dopamine), vascular parkinsonism, and toxin exposure (cyanide, carbon monoxide, carbon disulfide, and manganese) can be considered if historical details or neurological signs suggest them.

The diagnosis of PD is generally straightforward when all cardinal features are present, when the history of a slow progression and asymmetric onset are clear, and when there is a brisk response to dopaminergic therapy. Although most of the atypical cases usually have features that suggest diagnoses other than idiopathic PD, drug-induced parkinsonism is indistinguishable from PD clinically. Therefore, a close medication history, including current and past drug history to dopamine receptor blockers or dopamine depleting agents, is essential. Neuroimaging may be helpful to rule out a vascular etiology if the history suggests stepwise progression of symptoms. Dopamine transporter scans are available and help to identify groups of patients with low dopamine release [31], but in individual cases its utility to establish definitive PD is still controversial. The diagnosis of idiopathic PD follows the UK Brain Bank criteria, which requires bradykinesia and one additional cardinal motor feature [32]. Other disorders that may cause tremor and/or incoordination must also be considered in the differential, including but not limited to essential tremor and other forms of ataxia such as fragile X-associated tremor/ataxia syndrome.

Disease progression

The Hoehn and Yahr scale delineates five stages of disease, with stage 1 signifying unilateral involvement and stage 5 representing confinement to bed or wheelchair. Stage 3 (impaired postural reflexes) marks an important point in disease course, because the risk of falls emerges at this time although the patient is still physically independent. It is crucial to address fall precautions at all stages of the illness. In spite of this time-honored staging system, patients do not relentlessly follow a progression from stage 1 to 5, and at any one time most patients in a given clinical practice are stage 2 or 3 [33]. The primary role of therapy is to maintain patients in low stages without significant balance problems.

Mortality rates are higher in PD patients than in age-matched controls. Several factors have been debated to affect disease progression, such as age of onset, motor severity, and dementia, but no consensus has been reached [34]. The median survival time from motor onset to death has been reported to be up to 15.8 years [35]. Some authors have suggested that early prevention of motor progression and development of psychosis and dementia may be the most promising strategy to increase life expectancy in PD patients [35].

Management

Non-pharmacologic management

Education and patient-based interventions are important in the management of PD patients. Exercise has been well studied in PD and has been reported to be beneficial for strength, postural stability, balance, gait speed, physical functioning, and health-related quality of life [36]. In addition to documented improvements in motor function with exercise, epidemiologic evidence suggests that moderate to vigorous exercise may protect against PD [37]. Dietary modifications are also of particular interest, and various supplements are currently being studied for potential antioxidant properties (see below). Although maintaining a healthy, balanced diet is emphasized in the clinical setting, no studies have

Table 1.3 Therapeutics of PD.

Drug class	Mechanism of action
Levodopa	Aromatic amino acid that is decarboxylated to dopamine so that dopamine can stimulate central dopamine receptors
COMT inhibitors	Reversible inhibitor of catechol-*O*-methyltransferase, the enzyme that converts levodopa to an inactive compound Entacapone: acts on peripheral metabolism Tolcapone: acts on peripheral and central metabolisms
Dopamine agonists	Directly stimulate central dopamine receptors
MAO-B inhibitors	Irreversible inhibitor of monoamine oxidase type B, which is involved in oxidative deamination of dopamine in the brain
Amantadine	Thought to act as non-competitive antagonist at NMDA receptor, as well as to act as a partial dopamine agonist with mild anticholinergic effects
Anticholinergics	Muscarinic receptor antagonists, exerting effects in striatum to alter the functional dopamine-cholinergic balance

established an ideal "Parkinson's disease diet." However, particular attention must be paid to protein intake in patients on levodopa therapy (see below).

Pharmacologic management

Levodopa

Levodopa continues to be the gold standard of treatment in PD (Table 1.3). Levodopa is absorbed in the small intestine by an amino acid transporter system and is subsequently converted to dopamine by dopa-decarboxylase. Competition for this transporter system by dietary or supplementary large neutral amino acids may interfere with levodopa bioavailability. Therefore, protein restriction or redistribution in the diet may improve responsiveness [38]. In the periphery, levodopa is metabolized to dopamine by aromatic amino acid decarboxylase (AADC) and to 3-*O*-methyldopa by catechol-*O*-methyltransferase (COMT). This peripheral metabolism leads to several unwanted side effects, such as nausea, vomiting, and orthostasis. The co-administration of carbidopa, which is a peripheral decarboxylase inhibitor that does not cross the blood–brain barrier, works to limit these side effects and to increase plasma concentrations of dopa by limiting peripheral degradation. Levodopa is now almost exclusively available in combination with a peripherally active decarboxylase inhibitor (carbidopa/levodopa or benserazide/levodopa). Henceforth, in this chapter, reference to levodopa implies levodopa with a peripherally active decarboxylase inhibitor.

Although considered the most efficacious therapy, levodopa is often reserved for patients with more advanced disease or for those with immediate need for improvement (new falls, job security). The justification for withholding levodopa until significant disability develops is largely based on the relationship between levodopa exposure time/cumulative dose and side effects such as dyskinesias and motor fluctuations, as well as concerns of toxicity to dopaminergic neurons and progression of disease [38]. Dyskinesias are involuntary movements that range from dystonic to ballistic movements. Dyskinesias can be quite bothersome and, at times, disabling. Patients most often experience dyskinesias in the setting of being "on," that is, at the time when their medications are having their best effect in treating the parkinsonism (peak-dose dyskinesias). They may also rarely be present as medication begins to wear off, manifesting as dystonic leg cramps and spasms or flailing leg movements that may affect gait and balance, resulting in falls. Motor fluctuations refer to an unstable medication response, so that patients fluctuate with good ("on" periods) and poor ("off" periods) responses to their dopaminergic medications. As PD progresses, the amount of time a patient spends "on" decreases, and usually the duration of benefit from a given dose of levodopa shrinks so that, near the end of the dosing period, patients become more parkinsonian (wearing-off motor fluctuations). Alteration in doses of levodopa or frequency of dosing may help combat motor fluctuations. If the patient is not experiencing

side effects, an increase in dose may decrease the amount of time spent "off." Switching to a controlled-release formulation of levodopa may also be an option. However, if there are troublesome dyskinesias already present, it is typically more useful to decrease the dosing intervals in an attempt to deliver small but frequent quantities of levodopa throughout the day. In severe cases, tablets may be dissolved in liquid and sipped every hour through the course of the day.

New formulations of levodopa are being developed and tested, ranging from different types of non-oral products to oral products with combined short- and long-acting formulations to deliver more consistent blood levels of levodopa throughout the day. In addition, duodenal infusion of carbidopa/levodopa gel by a portable pump has been used in Europe for several years and is currently being studied in North America. A recent review examined randomized control trials that compared levodopa infusion therapies to best medical therapy, and showed significant benefit from levodopa infusion therapy in proportion of "on" time, activities of daily living, and motor scores [39].

COMT inhibitors

COMT inhibitors include entacapone and tolcapone, and they are used as adjunctive therapy with levodopa. These medications work to limit the peripheral degradation of levodopa and are only used in PD in conjunction with levodopa. Entacapone acts only on peripheral levodopa, while tolcapone can cross the blood–brain barrier and affect central metabolism. Both drugs work to increase the bioavailability of levodopa and have primarily been used to reduce motor fluctuations (wearing off). Dopaminergic side effects may be more pronounced when these drugs are introduced, mainly dyskinesias, nausea, and orthostatic hypotension. While diarrhea may be a side effect of either drug, urine discoloration may be apparent in a subset of patients on entacapone. Tolcapone is prescribed only to those patients who are unable to tolerate entacapone, due to the risk of potentially fatal acute fulminant liver failure. Close monitoring of liver function tests is recommended during treatment with tolcapone [38].

Dopamine agonists

Dopamine agonists (e.g., bromocriptine, pramipexole, ropinirole, cabergoline, piribedil, rotigotine, apomorphine) directly stimulate dopamine receptors, and have a different clinical and pharmacological profile than levodopa. Dopamine agonists do not compete for transport from the gut or at the blood–brain barrier and once present centrally act as direct agonists, without needing to be converted metabolically into dopamine. With the exception of apomorphine, these agents have a longer duration of action than levodopa. Additionally, some dopamine agonists have been studied as neuroprotective agents (see below). In North America and Western Europe, dopamine agonists are more often prescribed to PD patients before levodopa introduction in an attempt to delay dyskinesia onset. Agonists are often used in conjunction with levodopa. In a recent meta-analysis, dopamine agonists were shown to be more beneficial than COMT inhibitors and MAO-B inhibitors when used in combination with levodopa. Agonists showed superior reduction in "off" time and levodopa dose, as well as improved symptoms severity score [40].

Most agonists are available in pill form, and some have long-acting once-a-day formulations. Rotigotine is available only as a transdermal patch. Apomorphine is usually utilized as a subcutaneous injection for "rescue" therapy (see below).

There have been no head-to-head studies showing superior efficacy of one agonist over another. Valvular heart disease or pulmonary/retroperitoneal fibrosis may rarely be a complication of ergotamine dopamine agonist (e.g., bromocriptine, cabergoline, pergolide – withdrawn from market in 2007 because of valvular heart risk). Additionally, with all dopamine agonists, central side effects include confusion, hallucinations, and excessive daytime sleepiness, including sleep attacks. Daytime sleepiness is very important to monitor, because many PD patients are still driving. Compulsive behaviors and impulsive control disorders occur in a subset of patients on dopamine agonists. Patients may display behaviors such as excessive gambling, shopping, or hypersexuality. Punding, a stereotyped behavior characterized by non-goal-oriented, repetitive activity, may develop. In subjects with a past proclivity to such behaviors, dopamine agonists must be used with very careful monitoring, and even in subjects without past evidence of these traits, careful explanation and open dialog are important to patient management. When these behaviors occur, the usual treatment is reduction or withdrawal of the dopamine agonist.

Apomorphine differs from the other dopamine agonists in being a very short-acting dopamine D_1 and D_2 receptor agonist. Apomorphine is used as an injectable "rescue" medication in patients who

experience a sudden, unpredictable "off" or "freezing" episode in between their usual levodopa or other dopamine agonist doses [39]. In Europe, a continuous subcutaneous infusion of apomorphine is available. Interpretation of studies of apomorphine infusions is somewhat limited because of the small population size; however, a recent review concluded that apomorphine infusion therapy provides significant improvement in motor symptoms [39].

MAO-B inhibitors

Monoamine oxidase B (MAO-B) inhibitors irreversibly inhibit the enzyme that is responsible for the oxidative deamination of dopamine, thus increasing dopamine concentration in the brain. Selegiline and rasagiline make up the class of MAO-B inhibitors. Selegiline was the first to be approved by the US Food and Drug Administration (FDA) for the treatment of PD, and rasagiline followed 10 years later. The selectivity of selegiline for MAO-B is dose dependent, and therefore doses exceeding the recommended daily dose of 10 mg may result in non-selective MAO inhibition, placing the patient at risk for developing hypertensive crisis, due to dietary interactions with foods containing tyramine, also known as the "tyramine effect" [38]. In patients taking recommended doses of rasagiline, dietary restriction of most tyramine-containing products is not necessary, but foods high in tyramine should be avoided. The amphetamine and metamphetamine metabolites of selegiline are thought to contribute to clinically observed improvements in energy levels in some patients, but also may cause neuropsychiatric side effects and insomnia. When given with levodopa, both drugs can cause worsening of dopaminergic side effects, such as orthostatic hypotension and dyskinesias, as they enhance central dopamine stores. Additionally, co-administration of serotonergic agents, such as selective serotonin reuptake inhibitors (SSRIs), may place patients at greater risk for serotonin syndrome, a potentially fatal syndrome characterized by autonomic instability, neuromuscular excitability, and altered mental status. This syndrome appears to be markedly rare, but its severity warrants cautious introduction of either agent when used in conjunction with an SSRI.

Several studies have established clinical symptomatic benefits of MAO-B inhibitors in PD. In the Movement Disorder Society Evidence-Based Medical Review (MDS-EBMR) of treatments of PD, both selegiline and rasagiline are rated as *efficacious* as monotherapy [41]. There has been some suggestion of potential neuroprotective effects of this class of drugs. In the ADAGIO study, rasagiline (1 mg/day) introduced early in the course of PD was associated with less parkinsonian impairment compared to a group starting the drug later, but this effect was not seen with the same drug given at a higher daily dose (2 mg) [42]. This area of study remains poorly defined, and the MDS-EBMR report considered both agents to have insufficient evidence to ascribe any effect on prevention of clinical progression in early PD [41].

Amantadine

Amantadine, originally used as an antiviral agent, has demonstrated mild efficacy in PD. Although its mechanism of action is unclear, it is thought to act as a non-competitive antagonist at the *N*-methyl-D-aspartate (NMDA) receptor, with its therapeutic effect in PD possibly explained by its ability to interfere with excessive glutamate neurotransmission in the basal ganglia. It also has mild dopaminergic properties and anticholinergic effects. In the MDS-EBMR (2011), amantadine was rated as *likely efficacious* for treating the signs of PD as monotherapy and as an adjunct to levodopa [41]. It has also been established to reduce the severity of dyskinesias in PD [38]. Its use, however, is often limited by potential side effects including confusion, hallucinations, and a condition termed livedo reticularis, a diffuse mottling of the skin which typically involves the extremities. Since the drug is renally excreted, dose adjustments are necessary for patients with renal insufficiency.

Anticholinergics

Benztropine (benzatropine) and trihexyphenidyl are two centrally acting anticholinergic drugs used in the treatment of PD. These medications are used most commonly for their tremor-suppressing effects. The use of this class, however, is significantly limited because of side effects, including confusion, hallucinations, dry mouth, constipation, anhidrosis, blurred vision, and urinary retention. In certain populations, such as the elderly, cognitively impaired patients, and those with closed-angle glaucoma or prostatic hypertrophy, this class of drug should be avoided [38].

Surgical management

Deep brain stimulation (DBS) is an FDA-approved surgical treatment for medically refractory PD patients. A recent review of the DBS literature

concluded that DBS, in comparison to the best medical therapy, demonstrated a significant benefit in the amount of "on" time, activities of daily living, and motor scores. These improvements correlated with improvements in patient-related quality of life [40]. Unlike procedures previously performed, including pallidotomy and thalamotomy, DBS is reversible and programmable, and may be completed bilaterally. DBS involves electrical stimulation to specific nuclei through implanted electrodes. The selection of the targeting site is critical for the success of this therapy and should be based on an individual patient's needs. In PD the subthalamic nuclei (STN) and globus pallidus interna (GPi) are the preferred targets. Both targets improve the cardinal manifestations of PD and reduce motor fluctuations, dyskinesias, and dystonia [38]. One comparator trial reported similar outcomes in motor and quality of life outcomes with STN or GPi stimulation. Although the STN group showed greater reduction in PD medication after surgery, scores on cognitive processing speed were lower and depression was higher when compared to the GPi group [43]. While evidence suggests that DBS provides a beneficial effect up to five years [44], long-term follow-up data are sparse.

In addition to common post-surgical complications, adverse effects from hardware placement or stimulation must also be considered. The most common adverse events related to DBS hardware include infection migration or replacement of leads, lead fractures, and skin erosions. Stimulation-related adverse effects include dysarthria, gait and balance impairment, and depression. The literature is discrepant on the neuropsychological complications of DBS. Although there have been consistent reports of motor improvement with STN and GPi stimulation, the data on cognition and mood are more variable. With reports of an increased rate of post-surgical suicide, careful assessment and treatment both pre- and postoperatively is essential [45].

Treatment of non-motor complications

Much of the focus of this textbook will concern the behavioral non-motor elements of PD, and these are not discussed here. Dysphagia is a serious complication that may become more prominent with disease progression. The effects of dysphagia can lead to weight loss, malnutrition, and dehydration, and they may potentially be fatal if aspiration is occurring. Dysphagia along with immobility increases the risk for pneumonia, which is a frequent cause of death in PD patients. Treatment involves a multidisciplinary approach. It is important to refer patients to a speech therapist for appropriate evaluation and recommendations.

Sialorrhea (drooling) is a common occurrence in more advanced PD. Adequate treatment is important, as this accumulation of saliva may further increase risk of aspiration. Although anticholinergic and antihistaminergic medications have been used, side effects from these drugs are limiting. Botulinum toxin injection is now a more commonly used therapy.

Orthostatic hypotension may occur at any stage of PD. Initially non-pharmacologic interventions may be tried such as compression stockings, hydration, and increased sodium intake. If these measures are unsuccessful pharmacologic therapy (e.g., fludrocortisone, midodrine) may be considered.

Constipation may be one of the earliest non-motor symptoms reported by patients. Reviewing medications for possible contributors (e.g., anticholinergics) is essential. Ensuring adequate hydration and establishing a bowel regimen is important. When referring for further gastroenterological complications it is important to emphasize that dopamine blocking agents should be avoided.

Urologic complications include urinary/bladder dysfunction and erectile dysfunction. Urologic expertise may be sought to determine appropriate therapy for neurogenic bladder symptoms. Erectile dysfunction may be managed with a phosphodiesterase type-5 inhibitor, such as sildenafil [46].

Future perspectives

Whereas new therapies related to dopaminergic facilitation are in continual development, a large current research focus with evolving future programs concerns potential disease modification. Neuroprotective agents geared at slowing or halting disease progression are a priority in clinical research trials. A recent review outlined the various agents that have been studied, based on various proposed pathogenesis. Riluzole, a non-competitive NMDA receptor antagonist and inhibitor of presynaptic release of glutamate, has been studied for its potential role in excitotoxicity. The anti-apoptotic agents TCH346 (a properglyamine), CEP-1347 (a compound that inhibits mixed-lineage kinases), and minocycline