REVIEW ARTICLE

Parkinson Disease

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ABSTRACT

PURPOSE OF REVIEW: Parkinson disease is a common neurodegenerative disorder that affects millions of people worldwide. Important advances in the treatment, etiology, and the pathogenesis of Parkinson disease have been made in the past 50 years. This article provides a review of the current understanding of Parkinson disease, including the epidemiology, phenomenology, and treatment options of the disease.

RECENT FINDINGS: Parkinson disease is now recognized to be a heterogeneous condition marked by both motor and nonmotor symptoms. It is composed of preclinical, prodromal, and clinical phases. New medications with improved ease of administration have been approved for its treatment. Innovative surgical therapies for Parkinson disease may be used when motor symptoms persist despite optimal medical management.

SUMMARY: Parkinson disease is a complex, heterogeneous neurodegenerative disorder. Considerable progress has been made in its treatment modalities, both pharmacologic and surgical. While its cure remains elusive, exciting new research advances are on the horizon.

INTRODUCTION

Parkinson disease is a chronic, progressive, and disabling disorder that is characterized by both motor and nonmotor symptoms. The disease affects millions of people worldwide and is the second most prevalent neurodegenerative condition next to Alzheimer disease.[1] Patients experience progressive extrapyramidal motor symptoms, including tremor, bradykinesia, rigidity, imbalance, and a variety of nonmotor symptoms such as sleep and mood disorders. Despite its progressive nature, it remains one of the few neurodegenerative diseases whose symptoms can be readily treated with dopamine replacement therapy.

BRIEF HISTORY OF PARKINSON DISEASE

The English physician, James Parkinson, first characterized Parkinson disease in his 1817 monograph "An Essay on the Shaking Palsy."[2] Parkinson described several people who presented with resting tremor, shuffling gait, stooped posture, sleep problems, and constipation. He noted the progressive nature of the disease and the great disability it incurred and called it *paralysis agitans*. Charcot[3] later expounded on the disease, adding bradykinesia and rigidity to the constellation of symptoms, and renamed the condition *Parkinson disease*.

In the 1950s Carlsson[4] found that levodopa reversed reserpine-induced akinesia, paving the way for its use as a treatment for Parkinson disease. Cotzias

and colleagues[5] discovered that levodopa improved symptoms of Parkinson disease in 1967 when he administered DL-dihydroxyphenylalanine (DOPA) to patients with parkinsonism and achieved favorable results. Levodopa, when paired with carbidopa, became the mainstay of medical therapy and remains so to this day.

Significant advances were made in the latter part of the 20th century and in the 21st century regarding the physiologic mechanisms and additional treatment options for Parkinson disease. While levodopa continued to be the cornerstone of medical management, an association was made between high-dose levodopa, advanced disease progression, and the onset of motor fluctuations.[6,7] Dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors, and catechol-*O*-methyltransferase (COMT) inhibitors found a place in the therapeutic arsenal for the disease, along with novel forms of levodopa.

Surgical treatments for disease symptoms that were resistant to optimal medical management were also developed, including deep brain stimulation (DBS).

The 21st century has also witnessed remarkable discoveries in the genetic causes of Parkinson disease, while great strides have been made in the pathogenic mechanisms. Research continues to focus on potential neuroprotective and neurorestorative therapies.

KEY POINTS

- **A renaissance of therapeutic options for Parkinson disease have occurred in the last 50 years. Levodopa remains the gold standard for treatment of Parkinson disease, but dopamine agonists, monoamine oxidase type B inhibitors, catechol-*O*-methyltransferase inhibitors, and surgical procedures have greatly expanded the therapeutic options.**

- **Parkinson disease affects millions of people worldwide, and its prevalence increases greatly with advancing age.**

EPIDEMIOLOGY OF PARKINSON DISEASE

Parkinson disease affects millions of people worldwide, and the number of affected patients may double by 2030.[8] It is estimated that Parkinson disease affects about 1% of people older than 60 years of age in the United States.[9,10] The annual median age-standardized incidence rates of Parkinson disease in people older than 65 years of age in high-income countries is 160 per 100,000.[11] The lifetime risk of Parkinson disease is 2% in men and 1.3% in woman aged 40 years and older, when accounting for competing risks.[11] The incidence of Parkinson disease prior to age 50 is low but increases with advanced age. Men carry a greater chance of having Parkinson disease than women. The overall age-standardized incidence male-to-female ratio is estimated to be 1.46 (95% CI 1.24–1.72).[12] No area of the world is immune to Parkinson disease.

CLINICAL SYMPTOMS OF PARKINSON DISEASE

The motor and nonmotor symptoms of Parkinson disease are described below.

Motor Symptoms

The four cardinal motor symptoms of Parkinson disease are tremor, rigidity, bradykinesia, and postural instability, as identified by the acronym TRAP (tremor, rigidity, akinesia (or bradykinesia), and postural instability) (**TABLE 1-1**).[13] The secondary motor symptoms include diminished arm swing, decreased blink rate, masked facies (hypomimia), decreased voice volume (hypophonia), and difficulty turning over in bed.

Tremor refers to a rhythmic oscillation around a fixed point in the "rest" or nonpostural position. Tremor is often the first motor symptom of Parkinson disease and affects approximately 90% of patients at some point in their lives (**VIDEO 1-1**, *links.lww.com/CONT/A348*).[14] While the tremor of Parkinson disease is typically a resting tremor, 50% of patients may also present with a tremor than may reoccur with arms stretched outward.[14] Tremors start asymmetrically and are characterized by supination and pronation, or pill-rolling, eventually affecting

the opposite side of the body. Tremors may be less responsive to pharmacologic treatment, including levodopa.

Rigidity refers to stiffness or resistance of a limb when it is flexed passively, activating both agonist and antagonist muscles, and may also be referred to as cogwheeling.[15] Bradykinesia refers to slowness of movement (akinesia refers to lack of movement) and may occur during both initiation and continuation of movement.[16]

Postural instability, or balance dysfunction, is experienced later in the course of the disease, about a decade after initial diagnosis. Postural instability

TABLE 1-1 **Premotor, Nonmotor, and Motor Symptoms of Parkinson disease**

Premotor Symptoms

- Constipation
- Anosmia
- Rapid eye movement (REM) sleep behavior disorder
- Depression

Nonmotor Symptoms: Neuropsychiatric

- Depression
- Anxiety (mood disorders)
- Apathy
- Impulse control disorder
- Psychosis
- Anhedonia
- Hallucinations
- Abulia
- Attention deficit disorder
- Panic attacks

Nonmotor Symptoms: Cognitive

- Executive dysfunction
- Memory loss
- Dementia

Nonmotor Symptoms: Autonomic

- Orthostatic hypotension
- Constipation
- Fecal incontinence
- Nausea
- Vomiting
- Drooling

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correlates with disease severity and is elicited by the pull test. It is a levodopa-resistant symptom, in contrast to bradykinesia, rigidity, and tremor. Postural instability is a major cause of falls, contributing to hip fractures, loss of independence, and nursing-home placement in those afflicted by the disease.

Other terms related to Parkinson disease symptoms include *dyskinesia*, also called levodopa-induced dyskinesia, which refers to abnormal, involuntary, choreiform movements that may affect the limbs, head, and torso (**VIDEO 1-2**, *links.lww.com/CONT/A349*). Levodopa-induced dyskinesia may also manifest

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- Urinary incontinence and urgency
- Sexual dysfunction
- Altered cardiac reflexes
- Olfactory dysfunction
- Gastrointestinal dysfunction
- Increased sweating
- Dysphagia

Nonmotor Symptoms: Sleep Disorders

- Insomnia
- Somnolence
- Excessive daytime sleepiness
- Restless legs syndrome
- Sleep attacks
- Periodic limb movements of sleep
- REM sleep behavior disorder
- Vivid dreaming

Nonmotor Symptoms: Sensory Abnormalities

- Anosmia
- Pain
- Ageusia
- Numbness
- Paresthesia

Cardinal Motor Symptoms

- Tremor
- Rigidity
- Bradykinesia (or akinesia)
- Postural instability
- Gait disorder

with ballism, myoclonus, dystonia, or a combination of these movements.[17] Levodopa-induced dyskinesia may be further classified as peak-dose dyskinesia, wearing-off or off-period dyskinesia, or diphasic dyskinesia. Diphasic dyskinesia begins shortly after levodopa ingestion followed by improvement in parkinsonian symptoms and dyskinesia and a subsequent return of dyskinesia as dopamine levels decline.[14]

Dystonia refers to involuntary, prolonged muscle contractions with abnormal postures, usually in the limbs. Dystonia usually occurs in concert with lower dopamine levels, often in the early morning hours. Patients may experience toe curling or foot inversion due to dorsiflexion or plantar flexion of the lower extremity, possibly resulting in cramping or an aching of the affected leg. Dystonia may also occur in the peak-dose, diphasic, or "off" states (**VIDEO 1-3**, *links.lww.com/CONT/A350*).[18]

Motor fluctuations refer to "off" times, when poor response to levodopa alternates with "on" time, or improved function. Motor fluctuations occur with advancing disease, possibly due to fluctuating stimulation from levodopa on postsynaptic receptors.[19] Off periods may be either predictable, in which symptoms emerge prior to the next dose, or nonpredictable. Dose failure refers to levodopa that has a delayed clinical effect.[20] Freezing is described by Giladi and Nieuwboer[21] as "an episodic inability (lasting seconds) to generate effective stepping in the absence of any known cause other than parkinsonism or high-level gait disorders. It is most commonly experienced during turning and step initiation but also when faced with spatial constraint, stress, and distraction." Patients feel that their feet are glued to the ground, and this feeling is usually episodic in nature.

Nonmotor Symptoms

In the last 20 years, there has been increasing recognition of the importance of nonmotor symptoms (ie, symptoms other than those involved in movement, such as tremor, rigidity, and bradykinesia) in diagnosing and treating Parkinson disease. It is estimated that nearly all patients with Parkinson disease will experience several concurrent nonmotor symptoms throughout the course of the disease. The impact from nonmotor symptoms is often greater than that of motor symptoms; unfortunately, nonmotor symptoms are often underrecognized. The nonmotor symptoms of Parkinson disease are listed below and are included in **TABLE 1-1**.

- **Neuropsychiatric nonmotor symptoms including depression, apathy, impulse control disorders, anxiety, psychosis, hallucinations, mood disorders, apathy, and abulia**
- **Cognitive nonmotor symptoms including executive dysfunction, memory loss, and dementia**
- **Dysautonomia including orthostatic hypotension, constipation, urinary incontinence, sexual dysfunction, altered cardiac reflexes, olfactory dysfunction, gastrointestinal dysfunction, and sweating**
- **Sleep disorders including insomnia, somnolence, excessive daytime sleepiness, restless legs syndrome, sleep attacks, periodic limb movements of sleep, and rapid eye movement (REM) sleep behavior disorder**
- **Sensory abnormalities including pain, numbness, fatigue, and olfactory impairment[22]**

Nonmotor symptoms may also be subject to fluctuations. During off states, patients may experience worsening in mood, anxiety, dysautonomia including

sweating and temperature irregularities, pain/numbness, and other symptoms (CASE 1-1). Nonmotor on states may include mania, agitation, delusions, paranoia, and impulsivity.[23]

Premotor Symptoms

Premotor symptoms are defined as symptoms that predate motor symptoms of Parkinson disease and include constipation, anosmia, REM sleep behavior disorder, and depression (TABLE 1-1).[25]

DIAGNOSIS OF PARKINSON DISEASE

Parkinson disease remains a clinical diagnosis. The asymmetric symptoms of resting tremor, bradykinesia, and rigidity with favorable response to dopaminergic therapy suggest its diagnosis. Exclusionary features may include severe dysautonomia, early hallucinations, dementia preceding motor symptoms, and postural instability and freezing within the first 3 years after diagnosis (CASE 1-2).[27] The UK Parkinson's Disease Society Brain Bank Diagnostic Criteria[28] are listed in TABLE 1-2.[29]

CLINICAL PROGRESSION OF PARKINSON DISEASE

Parkinson disease is a neurodegenerative progressive disease. The Movement Disorder Task Force recently recognized three stages in early Parkinson disease[14,30,31]: (1) the preclinical phase, in which neurodegeneration begins but patients lack clinical symptoms; (2) the prodromal phase, in which symptoms are present but are insufficient to make a diagnosis of Parkinson disease; and (3) the clinical phase, in which parkinsonian symptoms are manifest and recognizable.

While it is difficult to accurately predict the general disease progression, motor fluctuations usually affect patients within 5 to 10 years after diagnosis, while postural instability occurs after about 10 years. Patients usually have a "good" period early on after diagnosis, in which they benefit from dopaminergic therapy. However, the disease is eventually marked by uneven response to levodopa, motor complications and fluctuations, levodopa-induced dyskinesia, speech and swallowing deficits, freezing, falls, and imbalance. Patients with younger-onset disease are more prone to levodopa-induced dyskinesia and motor fluctuations, while patients with older-onset disease have more cognitive issues and dysautonomia.[32]

DIFFERENTIAL DIAGNOSIS OF PARKINSON DISEASE

The diagnosis of Parkinson disease may be complex, and it is estimated that approximately 25% of patients have been misdiagnosed with another disease. The differential diagnosis of Parkinson disease includes tremor syndromes, such as essential tremor, atypical parkinsonisms (previously known as Parkinson-plus syndromes), as well as other tremor disorders, secondary parkinsonisms, and other cognitive disorders.

Perhaps the most difficult differential diagnoses for Parkinson disease are the atypical parkinsonisms. Red flags for atypical parkinsonisms include early speech difficulties, imbalance, a lack of tremor (generally), symmetry of symptoms (except for corticobasal degeneration), and a poor response to levodopa. The atypical parkinsonisms include progressive supranuclear palsy, corticobasal degeneration, diffuse Lewy body diseases, and multiple system atrophy

KEY POINTS

- Clinical features of Parkinson disease include tremor, rigidity, akinesia (or bradykinesia), and postural instability. Nonmotor symptoms are commonly experienced by patients and often negatively impact quality of life. Premotor symptoms include constipation, anosmia, rapid eye movement sleep disorder, and depression.
- The diagnosis of Parkinson disease is made clinically. Red flags for atypical parkinsonism include severe dysautonomia, early-onset hallucinations and dementia, freezing, postural instability, and lack of response to levodopa. Red flags for atypical parkinsonism also include early speech difficulties and imbalance, poor response to levodopa, and symmetrical symptoms.
- Parkinson disease may be divided into preclinical, prodromal, and clinical phases. Patients generally experience good response to levodopa for several years following their diagnosis.

CASE 1-1

A 72-year-old woman presented for evaluation of worsening Parkinson disease symptoms, including tremor, bradykinesia, and rigidity that she had experienced over the past year. She had been diagnosed with Parkinson disease 6 years prior after developing an asymmetric resting tremor and rigidity. She was placed on carbidopa/levodopa at that time, and she had a definite and clear motor response to the medication. The patient noticed worsening symptoms of bradykinesia and rigidity in the past 2 years that required an increase in her carbidopa/levodopa immediate-release dose.

The patient reported lightheadedness upon rising from a chair several times a week along with fatigue and mild confusion. These symptoms occurred more frequently in the summer months and when she became overheated. She also reported heat and cold intolerance, urinary frequency, and constipation. Blood pressure readings taken several times a week with a home monitor recorded occasional drops in systolic blood pressure of more than 20 mm Hg within a few minutes of standing, with no compensatory increase in pulse.

Four years after her initial diagnosis of Parkinson disease, she was referred to a cardiologist, who diagnosed her with autonomic dysfunction, secondary to Parkinson disease. The patient made an effort to stay hydrated, especially in hot weather. She wore elasticized stockings, started to exercise more, and monitored her blood pressures daily.

Her health was otherwise good, and her physical examination, urinalysis, laboratory tests, and brain MRI had been normal. Her medications included carbidopa/levodopa 25 mg/100 mg 1.5 tablets 4 times a day and vitamins.

On current examination, the patient had mild bradykinesia, moderate rigidity in the right arm and leg, mild rigidity in the left arm and leg, and a mild resting tremor in her right hand. Mild hypophonia and hypomimia were present. Her gait consisted of a mildly narrow base and shortened strides, with mild en bloc turning. Supine and standing blood pressure and pulse readings did not show current significant orthostasis (120/80 mm Hg supine with a pulse of 70 beats/min, and 105/60 mm Hg standing with a pulse of 72 beats/min.

COMMENT

Autonomic dysfunction occurs in Parkinson disease and includes cardiovascular, gastrointestinal, urologic, thermoregulatory, and sexual dysfunction. One misconception is that the presence of autonomic dysfunction occurs only in patients with multiple system atrophy, or atypical parkinsonism. Autonomic dysfunction also affects many patients with idiopathic Parkinson disease as well. While carbidopa/levodopa can cause orthostatic hypotension, the disease process itself is often the root cause.[24] Symptoms of autonomic dysfunction are important to recognize in Parkinson disease as they may be treatable.[24]

CASE 1-2

A 60-year-old man presented to a movement disorder center for initial evaluation of a right-sided resting tremor and stiffness that had begun 2 years earlier. The tremor started insidiously but worsened with time. He was not bothered by his symptoms. The patient's past medical history was significant for hypertension. He reported olfactory loss and constipation that began about 10 years ago.

Examination revealed a well-developed man who had mild bradykinesia along with a right-sided (arm and leg) resting tremor and rigidity. No rigidity or resting tremor was noted on his left side. Secondary symptoms of hypophonia and hypomimia were present. Right-sided finger taps, pronation-supination, hand movements, and toe tapping were noticeably diminished. His gait revealed a mild right leg drag with decreased right arm swing. No postural instability was noted. His vital signs and his physical and general neurologic examination were otherwise normal. A brain MRI performed by a previous neurologist was reviewed and was unremarkable.

The patient was diagnosed with Parkinson disease. Potential treatment options were discussed with the patient, including dopamine agonists, anticholinergic medications, carbidopa/levodopa, monoamine oxidase inhibitors, or a regimen of exercise without medication. While he did not receive symptomatic treatment for the motor symptoms of the disease, he agreed to be treated for constipation and to continue his exercise regimen.

COMMENT

The patient received a diagnosis of clinically established Parkinson disease. The Movement Disorder Society Task Force describes parkinsonism as "bradykinesia, in combination with either rest tremor, rigidity, or both."[26] After parkinsonism is established, the task at hand is to determine whether parkinsonism is actually caused by Parkinson disease. The diagnosis of clinically established Parkinson disease requires at least two supportive criteria, which in this case are olfactory loss and resting tremor of a limb, as well as the "absence of absolute exclusion criteria and no red flags." The exclusion criteria for Parkinson disease were also met, including the absence of cerebellar abnormalities, downward vertical gaze palsy, behavioral variant of frontotemporal dementia or primary progressive aphasia, parkinsonian symptoms that are restricted to the lower limbs for more than 3 years, drug-induced parkinsonism, and unequivocal cortical sensory loss. No red flags for an alternative diagnosis were apparent, such as rapid gait impairment, bulbar dysfunction, severe autonomic failure, or recurrent falls. He also experienced prodromal symptoms of Parkinson disease, including olfactory loss.

The patient decided against pharmacotherapy but was encouraged to exercise. Evidence supports that patients with Parkinson disease obtain short-term and long-term benefits from exercise, including improvements in motor and nonmotor symptoms of the disease.

TABLE 1-2

UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria[a]

Step 1: Diagnosis of Parkinsonian Syndrome

- **Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)**
- **And at least one of the following:**
  - Muscular rigidity
  - 4–6Hz resting tremor
  - Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2: Exclusion Criteria for Parkinson Disease

- **History of repeated strokes with stepwise progression of parkinsonian features**
- **History of repeated head injury**
- **History of definite encephalitis**
- **Oculogyric crises**
- **Neuroleptic treatment at onset of symptoms**
- **More than one affected relative**
- **Sustained remission**
- **Strictly unilateral features after 3 years**
- **Supranuclear gaze palsy**
- **Cerebellar signs**
- **Early severe autonomic involvement**
- **Early severe dementia with disturbances of memory, language, and praxis**
- **Babinski sign**
- **Presence of a cerebral tumor or communicating hydrocephalus on CT scan**
- **Negative response to large doses of levodopa (if malabsorption excluded)**
- **MPTP exposure**

Step 3: Supportive Prospective Positive Criteria for Parkinson Disease

- **Three or more required for diagnosis of definite Parkinson disease**
  - Unilateral onset
  - Resting tremor present
  - Progressive disorder
  - Persistent asymmetry affecting the side of onset most
  - Excellent response (70–100%) to levodopa
  - Severe levodopa-induced chorea
  - Levodopa response for 5 years or more
  - Clinical course of 10 years or more

CT = computed tomography; MPTP= 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

[a] Reprinted with permission from Gibb WR and Lees AJ, J Neurol Neurosurg Psychiatry.[29] © 1988 BMJ Publishing Group Ltd.

(cerebellar or parkinsonian type, MSA-C and MSA-P, respectively). The atypical parkinsonisms usually include another prominent symptom aside from motor dysfunction, such as dysautonomia (MSA-C and MSA-P), supranuclear gaze palsy, and marked asymmetry/dystonia of one limb with cortical findings (corticobasal degeneration).[33]

KEY POINT

● Parkinson disease is characterized by the loss of dopaminergic neurons and the presence of Lewy bodies containing the misfolded protein α-synuclein.

ETIOLOGY OF PARKINSON DISEASE

Parkinson disease is characterized by the loss of dopaminergic neurons in the nigrostriatal system and by the presence of Lewy bodies in the brainstem. Motor symptoms become evident when 60% to 80% of dopaminergic neurons are lost in the pars compacta of the substantia nigra.[34]

It appears that Parkinson disease is actually a heterogeneous disorder characterized by various clinical presentations, age of onset, types of nonmotor symptoms, and different rates of progression.[35] While some patients have a relatively benign disease course with favorable response to dopaminergic therapy, others appear to progress more rapidly. Many patients have a preponderance of nonmotor symptoms while others do not.[36]

Genetic Causes of Parkinson Disease

Parkinson disease is likely caused by multiple factors that lead to the deterioration of dopaminergic neurons. It is estimated that 5% to 10% of patients have a genetic etiology for the disease. Monogenic forms of Parkinson disease include PARK-SNCA, PARK-LRRK2, and PARK-VPS35, among others.

Another genetic risk factor for Parkinson disease and for the Ashkenazi Jewish population in particular is the glucocerebrosidase, or *GBA1*, the gene responsible for Gaucher disease. *GBA1* directs the production of the glucocerebrosidase protein, which is involved in lysosomal activity. A genetic defect in *GBA1* causes a reduction in glucocerebrosidase activity, an increase in glucosylceramide, and promotion of α-synuclein accumulation, leading to a a greater chance of developing Parkinson disease.

The advancement of genetic research with whole exome genetic sequencing should provide future directions in genetic causes of Parkinson disease, including a greater understanding of pathogenetic etiologies.[37,38]

Environmental Causes of Parkinson Disease

Interest in whether environmental or toxic exposures can contribute to the development of Parkinson disease was sparked by the association between 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a prodrug to the neurotoxin MPP+, and parkinsonism during the 1980s.[38] Some of the environmental factors and toxic exposures that may be associated with Parkinson disease include pesticides (rotenone and paraquat); heavy metals (manganese, lead, and copper); well water; woodworking; head injury; other substances including polychlorinated biphenyls, trichloroethylene, perchloroethylene, and carbon tetrachloride; and rural living. Exposure to toxins, including carbon monoxide, trace metals, organic solvents, and cyanide have also been implicated as environmental risk factors. Alternatively, smoking and caffeine intake are thought to reduce disease risk, although further studies are ongoing.[12,14]

NEUROIMAGING OF PARKINSON DISEASE

Neuroimaging technology such as the dopamine transporter single-photon emission computed tomography (SPECT) scan may be helpful in making a diagnosis of Parkinson disease. In 2011, the US Food and Drug Administration approved dopamine transporter SPECT using ioflupane I-123 injection.[39] Dopamine transporter SPECT has a high sensitivity (87% to 98%) and specificity (80% to 100%) when differentiating Parkinson disease from essential tremor[40–44] and is considered an adjunct to diagnostic assessments. However, dopamine transporter SPECT is not a confirmatory test for Parkinson disease, nor is it intended to differentiate between Parkinson disease and other degenerative forms of parkinsonism, including atypical parkinsonism. Clinicians may decide to order a dopamine transporter SPECT when the diagnosis of a clinical tremor syndrome is uncertain (eg, when differentiating between Parkinson disease and essential tremor).

CLINICAL RATING SCALES FOR PARKINSON DISEASE

Clinical rating scales are useful to follow the progression of Parkinson disease and are used in clinical trials. The Unified Parkinson's Disease Rating Scale (UPDRS),[45] recently revised to the Movement Disorder Society-Sponsored Revision (MDS-UPDRS),[46] is a commonly used and validated research scale that contains four parts: cognition and mood, activities of daily living, motor examination, and motor complications. The Unified Dyskinesia Rating Scale (UDysRS) is used to evaluate abnormal involuntary movements, or dyskinesia, that occur with advancing Parkinson disease.[47] The Hoehn and Yahr Scale describes five stages of Parkinson disease: unilateral symptoms, bilateral symptoms, postural instability with worsening bilateral symptoms, worsening symptoms with the inability to live alone or independently, and wheelchair or bed assistance.[48] Other clinical rating scales commonly used are the Schwab and England Activities of Daily Living Scale,[49] the Parkinson's Disease Questionnaire (PDQ-39 and PDQ-8),[50] and the Parkinson's Disease Non-motor Symptoms (PD NMS) Questionnaire.[51] Patient diaries may provide invaluable information on motor fluctuations in relation to medication intake,[52] and kinematic sensors may use new technology to detect and measure motor fluctuations in the future.[53]

PHARMACOLOGIC AGENTS FOR PARKINSON DISEASE

Levodopa is the gold standard for dopamine replacement therapy in Parkinson disease. It is administered with a dopa decarboxylase inhibitor (carbidopa) to reduce its peripheral breakdown and lessen nausea. Levodopa is particularly effective in treating akinesia and rigidity, with more variable effects on tremor.[14] Clinical research suggests that levodopa treatment does not worsen disease progression.[54]

Carbidopa/levodopa is available as immediate-release, extended-release, and orally disintegrating tablets. A newer formulation of extended-release carbidopa/levodopa (IPX066) was designed for rapid absorption, ease of administration, and longer duration of clinical benefit[55,56] (**TABLE 1-3**). IPX066 has clinically been shown to improve on time without troublesome dyskinesia time while reducing off time in advanced Parkinson disease.[55,56] A

levodopa inhalation powder has also been FDA-approved for intermittent treatment of off episodes in patients with Parkinson disease who take carbidopa/levodopa.

Another formulation of levodopa is levodopa/carbidopa intestinal gel, which provides continuous infusion using a percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) tube.[57] Clinical trials have shown that levodopa/carbidopa intestinal gel reduces plasma levodopa fluctuations and off time and increases on time without troublesome dyskinesia compared to oral medication in patients with advanced disease.[58] Levodopa/carbidopa intestinal gel may be recommended for patients with Parkinson disease who experience motor fluctuations and dyskinesia who cannot be optimally treated with oral medication. Patients with advanced Parkinson disease who are not candidates for surgical management may also benefit from levodopa/carbidopa intestinal gel. Adverse events secondary to levodopa/carbidopa intestinal gel usually pertain to issues with the PEG-J. There are reports of polyneuropathy (either a sensory polyneuropathy or a more severe neuropathy resembling Guillain-Barré syndrome) in some patients who have received levodopa/carbidopa intestinal gel.[59]

Dopamine agonists directly stimulate dopamine receptors, thereby bypassing degenerating dopaminergic neurons in the brain. Non–ergot dopamine agonists are used as both monotherapy and adjunctive therapy in the treatment of Parkinson disease. They have longer half-lives (greater than 6 hours) than levodopa, but also have a higher incidence of psychiatric side effects, including hallucinations and impulse control disorders as well as potential "sleep attacks" (ie, episodes of sudden onset of sleep). Dopamine agonists include pramipexole, ropinirole (available in immediate-release and extended-release formulations), rotigotine (transdermal formulation), and apomorphine for subcutaneous use as a rescue medication for acute off periods.

COMT inhibitors reduce the breakdown of levodopa to 3-*O*-methyldopa and increase the plasma half-life of levodopa and its area under the curve.[60] COMT inhibitors are used in conjunction with levodopa to improve end-of-dose wearing-off time, although they may increase dyskinesia. Currently available COMT inhibitors include entacapone and tolcapone, a COMT inhibitor that carries a black box warning for potential liver toxicity.[61–63]

MAO-B inhibitors prevent levodopa degradation in the brain and limit its reuptake. They were initially thought to provide antioxidative properties in patients with Parkinson disease. Selegiline is a selective and irreversible MAO-B inhibitor approved as adjunctive medication to levodopa in patients with motor fluctuations. Rasagiline, a second-generation MAO-B inhibitor, lacks the amphetamine metabolites of selegiline and may be used as monotherapy and adjunct therapy. Safinamide is another potent, reversible MAO-B inhibitor that has been recently approved as adjunct therapy in patients with Parkinson disease with motor fluctuations.[64]

An *N*-methyl-D-aspartate (NMDA) receptor antagonist, amantadine, was originally used as an antiviral medication in the 1960s and has antidyskinetic properties. A newer preparation of amantadine, ADS-5102, is an extended-release form of amantadine that may be used to treat levodopa-induced dyskinesia in patients with Parkinson disease.[65]

KEY POINTS

- **Parkinson disease remains a clinical diagnosis. Neuroimaging techniques such as dopamine transporter single-photon emission computed tomography are helpful in differentiating between essential tremor and tremor from parkinsonian syndromes.**
- **Clinical rating scales and patient diaries are helpful in monitoring disease progression and are useful tools in clinical research trials.**

TABLE 1-3 **Pharmacologic Treatment of Parkinson Disease**

Name	Class	Dosage Strength	Administration	Indication
Carbidopa/ levodopa immediate release	Levodopa	25 mg/100 mg;10 mg/ 100 mg; 25 mg/250 mg	Oral	Treatment of Parkinson disease (PD) symptoms
Carbidopa/ levodopa extended release	Levodopa	50 mg/200 mg; 25 mg/100 mg	Oral	Treatment of PD symptoms
Carbidopa/ levodopa orally disintegrating	Levodopa	25 mg/100 mg; 10 mg/100 mg; 25 mg/250 mg	Sublingual	Treatment of PD symptoms
Carbidopa/ levodopa extended-release capsules	Levodopa	23.75 mg/95 mg; 36.25 mg/ 145 mg; 48.75 mg/195 mg; 61.25 mg/245 mg	Oral	Treatment of PD symptoms
Carbidopa/ levodopa enteral suspension	Levodopa	4.63 mg/mL carbidopa and 20 mg/mL levodopa; 100 mL total in one cassette for infusion	Enteral	Treatment of motor fluctuations in advanced PD
Levodopa inhalation powder	Levodopa	84 mg, 168 mg, 252 mg, 336 mg, 420 mg	Oral inhalation	Intermittent treatment of off episodes in patients with PD using carbidopa/levodopa
Carbidopa/ levodopa/ entacapone	Levodopa plus catechol-*O*-methyltransferase (COMT) inhibitor	12.5 mg/50 mg/200 mg; 18.75 mg/ 75 mg/200 mg; 25 mg/100 mg/ 200 mg; 31.25 mg/125 mg/200 mg; 37.5 mg/150 mg/200 mg; 50 mg/ 200 mg/200 mg	Oral	Indicated for end-of-dose wearing off
Pramipexole immediate release	Dopamine agonist	0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg	Oral	Treatment of PD symptoms
Pramipexole extended release	Dopamine agonist	0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, 4.5 mg	Oral	Treatment of PD symptoms
Ropinirole immediate release	Dopamine agonist	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg	Oral	Treatment of PD symptoms
Ropinirole extended release	Dopamine agonist	2 mg, 4 mg, 6 mg, 8 mg, 12 mg	Oral	Treatment of PD symptoms
Rotigotine	Dopamine agonist	2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours	Transdermal patch	Treatment of PD symptoms
Apomorphine hydrochloride	Dopamine agonist	0.2 mL (2 mg)–0.6 mL (6 mg)	Subcutaneous	Acute, intermittent treatment of hypomobility, off episodes (end-of-dose wearing off and unpredictable on/off episodes) associated with advanced Parkinson disease

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Name	Class	Dosage Strength	Administration	Indication
Entacapone	COMT inhibitor	200–1600 mg (200 mg/d–200 mg up to 8 times per day) in conjunction with levodopa/ carbidopa	Oral	Adjunct to levodopa therapy in patients with PD with end-of-dose wearing off
Tolcapone	COMT inhibitor	100 mg 3 times a day–200 mg 3 times a day in conjunction with levodopa/carbidopa	Oral	Adjunct to levodopa therapy in patients with PD with end-of-dose wearing off
Selegiline	Monoamine oxidase type B (MAO-B) inhibitor	10 mg/d (5 mg 2 times a day, breakfast and lunch)	Oral	Adjunct to levodopa therapy in patients with PD who experience a deterioration in positive response to the levodopa therapy
Selegiline oral disintegrating	MAO-B inhibitor	1.25 mg, 2.5 mg	Sublingual	Adjunct to levodopa therapy in patients with PD who experience a deterioration in positive response to the levodopa therapy
Rasagiline	MAO-B inhibitor	0.5 mg, 1 mg; monotherapy: 1 mg	Oral	Treatment of PD symptoms: monotherapy and adjunctive therapy with levodopa
Safinamide	MAO-B inhibitor	50 mg/d, 100 mg/d	Oral	Indicated as an add-on therapy for those taking carbidopa/ levodopa for off time
Amantadine immediate release	*N*-methyl-D-aspartate (NMDA) antagonist	100 mg capsules or tablets	Oral	Medications for treatment of Parkinson disease
Amantadine extended-release capsule	NMDA antagonist	137 mg, 274 mg	Oral	Treatment of dyskinesia in patients with PD receiving levodopa therapy
Amantadine extended-release tablet	NMDA antagonist	129 mg, 193 mg, 258 mg	Oral	Treatment of dyskinesia in patients with PD receiving levodopa therapy
Trihexyphenidyl	Anticholinergic	2 mg, 5 mg	Oral	Used to treat tremor in Parkinson disease
Benztropine	Anticholinergic	0.5 mg	Oral	Used to treat tremor in Parkinson disease

Anticholinergic medications such as trihexyphenidyl and benztropine were the original drugs used to treat Parkinson disease. They are used to treat tremor in younger patients with Parkinson disease as their side effects include confusion, dry mouth, urinary retention, and constipation.

TREATMENT OF PARKINSON DISEASE

A number of therapeutic options exist for Parkinson disease. Treatment options must be targeted to both motor and nonmotor symptoms. Management of patients may differ depending on disease severity and duration.

CASE 1-3

A 75-year-old woman presented for evaluation of an arm tremor. The patient's primary care physician observed a right-sided resting tremor during a routine well care visit earlier that year and referred her to a movement disorders center for evaluation. She dragged her right leg when walking and reported stiffness and pain in her right arm and leg. She reported daytime somnolence due to a long history of insomnia, and described mild forgetfulness.

On examination, the patient was mildly hypertensive, but her vital signs and physical examination were otherwise normal. Her Mini-Mental State Examination was 27 out of 30. The patient had moderate bradykinesia, moderate resting tremor in her right hand, and mild resting tremor in her left hand, with rigidity noted in all limbs. She had moderately stooped axial posture, and she had a narrow-based gait with shortened strides. The patient took several steps back on the pull test but recovered unaided.

The patient was diagnosed with Parkinson disease. She was placed on carbidopa/levodopa 25 mg/100 mg, 1 tablet 4 times daily, with tablets taken before meals. She returned to clinic after 6 weeks with marked improvement in motor symptoms.

COMMENT

The patient had Parkinson disease and exhibited the cardinal symptoms of bradykinesia, resting tremor, and rigidity. She demonstrated supportive criteria for the disease as well as the absence of exclusionary criteria and red flags. The symptoms were bothersome to the patient, so treatment was appropriate.

Levodopa remains the gold standard of treating Parkinson disease and is the single most effective agent to treat all stages of the disease.[70] The patient was in her midseventies, had mild cognitive impairment and excessive daytime sleepiness, and was clearly in need of dopaminergic therapy.

Dopamine agonists were not used in this case as they can worsen excessive daytime sleepiness and exacerbate neuropsychiatric symptoms. Anticholinergic medications might improve her tremor, but will do little for the bradykinesia and rigidity she experiences, and patients who are 70 years of age and older may also be more prone to experiencing side effects from their use.

Early Parkinson Disease

Treatment of Parkinson disease consists of a dopamine replacement strategy to improve disease symptoms, as neuroprotective therapies are not yet available. Patients should be offered dopaminergic treatment when their symptoms become bothersome. There is no known benefit of withholding treatment from patients who have disease symptoms.[66]

When a patient is newly diagnosed with Parkinson disease, it is important to determine whether symptoms are bothersome enough to the patient to warrant treatment while also keeping nonmotor symptoms in mind. Factors to be taken into consideration are the patient's age, comorbid conditions, employment status, and other quality-of-life issues. For example, has the patient presented to a neurology clinic to obtain a diagnosis, a second opinion, or for symptom treatment?

A discussion about treatment of early Parkinson disease requires a short review regarding the controversy over initiating levodopa treatment in younger patients. Levodopa is a safe and efficacious medication for practically reversing disease symptoms for a period of time. Motor fluctuations and dyskinesias may be more closely associated with longer disease duration and higher levodopa daily dose rather than the duration of levodopa therapy.[67] Pulsatile delivery of levodopa also contributes to dyskinesia.[68] As the disease progresses, higher and more frequent doses of levodopa are required. While no definitive evidence indicates that levodopa induces cell death, symptomatic therapy should be initiated while also considering both short-term and long-term potential side effects.[66]

Dopamine agonists, MAO-B inhibitors, or anticholinergic medications may be initiated in patients with Parkinson disease who are younger than 70 years of age. However, non–levodopa medications eventually will be insufficient to effectively ameliorate motor symptoms, and patients will need to be treated with levodopa (levodopa rescue).

Treatment of younger patients with levodopa should be considered if symptoms are bothersome enough to cause suffering or interfere with qualify of life. Younger patients may need more effective control of their symptoms with levodopa if they need to remain employed or have other responsibilities including childcare or eldercare. Patients may also be unable to receive optimal treatment with non–levodopa agents because of untoward side effects. Several studies suggest that starting treatment with levodopa leads to better long-term motor outcomes and better functioning long-term.[20] In older patients with evidence of cognitive decline, excessive daytime sleepiness, or other comorbid conditions, it is more appropriate to initiate treatment for Parkinson disease with levodopa. Dopamine agonists, MAO-B inhibitors, and anticholinergic medications are more likely than levodopa to cause cognitive side effects in the elderly.

Exercise should be encouraged for all patients with Parkinson disease as long as it is performed safely. Some evidence suggests that long-term aerobic exercise may slow Parkinson disease progression.[69] Studies to confirm this hypothesis are ongoing.[19] Exercise modalities include core strength training exercises, tai chi, yoga, boxing, and dance and music therapy. Cognitive training with puzzles and computer games should also be encouraged (CASE 1-3).

KEY POINTS

- **While levodopa is the gold standard in the treatment of Parkinson disease, it is now available in several formulations that may provide ease of administration and improved efficacy. Other available medications are dopamine agonists, catechol-*O*-methyltransferase inhibitors, monoamine oxidase type B inhibitors, an *N*-methyl-D-aspartate antagonist, and anticholinergic medications.**
- **Patients with Parkinson disease should be offered dopaminergic treatment when their symptoms are bothersome. Patients with Parkinson disease should be encouraged to exercise, as long as it is performed safely.**

Advanced Parkinson Disease

As Parkinson disease advances, the reduced storage and release capacity of endogenous dopamine can lead to the shortened duration of levodopa benefit. Patients will experience a decline in medication efficacy in which symptoms return prior to the next dose, referred to as predictable wearing off. Motor fluctuations and levodopa-induced dyskinesia set in, and in time may occur with troublesome dyskinesia for much of the waking day. Motor fluctuations may be caused by pulsatile stimulation of dopamine receptors. Gastric emptying issues with advanced disease may further contribute to uneven medication absorption. Nonmotor fluctuations may occur as well, including depression, fatigue, and anxiety.

The aim of Parkinson disease treatment is to optimize on time and reduce off time while minimizing troublesome levodopa-induced dyskinesia. Off time may be treated by taking Parkinson disease medications more frequently, using an extended-release form of levodopa, adding a COMT inhibitor or MAO-B inhibitor, or by the addition of a dopamine agonist to provide a more stable response.

Treatment of levodopa-induced dyskinesia requires identifying its occurrence in relation to levodopa dosing. Redistribution of medication doses, as well as changing forms of medication from immediate-release to extended-release formulations, for example, may improve motor fluctuations and levodopa-induced dyskinesia. Amantadine has been shown to treat levodopa-induced dyskinesia and is now available as an extended-release formation, which has been shown to reduce levodopa-induced dyskinesia and off time.[65] In patients with advanced Parkinson disease who are suboptimally treated despite best medical practice using oral medications, levodopa/carbidopa intestinal gel or surgical management may be considered.

Surgical Treatment of Parkinson Disease

Surgical treatment of Parkinson disease was developed for patients who, despite medication optimization, experience motor symptoms that cannot be satisfactorily ameliorated by medication. A common surgical treatment is DBS, which targets the subthalamic nucleus, globus pallidus internus, or ventral intermediate nucleus of the thalamus for tremor-predominant Parkinson disease with otherwise minimal symptoms. DBS involves modulating the brain circuitry using electrical stimulation from an implanted current source.[71] It has been demonstrated to improve tremor, dyskinesia, and motor fluctuations and has been used to treat thousands of patients with Parkinson disease worldwide.

DBS is a programmable procedure, and patient selection and accurate implantation at the optimal target are keys for surgical success. Many centers consider 75 years of age or even slightly older to be an approximate upper limit.[72] Most DBS procedures are performed about 10 years after diagnosis, but the EARLYSTIM (Controlled Trial of Deep Brain Stimulation in Early Patients with Parkinson's Disease) trial suggests that DBS may be used earlier in the course of the disease.[73] Exclusionary criteria for DBS include the presence of an atypical parkinsonism, unstable psychiatric disease, advanced disease with significant dementia, comorbidities that preclude surgical candidacy, and advanced age. Patients typically receive neuropsychiatric evaluation prior to surgery to assess their suitability for surgery and estimate their risk of cognitive

impairment. Patients also receive medical clearance and imaging with MRI to identify strokes, atrophy, or other abnormalities that could interfere with successful lead placement.

Surgical planning for DBS typically involves preoperative imaging including an MRI of the brain. The target is identified via patient-specific anatomy (so-called direct targeting) with or without reference to the consensus stereotactic coordinates established for each target (so-called indirect targeting), and a trajectory is planned to avoid vascular and other critical intracranial structures. Lead placement may be further refined using microelectrode recording with or without stimulation mapping.[71] DBS electrodes are implanted into the appropriate cerebral target causing a microlesion, and an implanted pulse generator is placed under the skin near the clavicle. Several weeks after surgery, when the microlesion effect has subsided, the implanted pulse generator is programmed with stimulation parameters designed to deliver current to the appropriate areas to improve symptoms.[74] The patient returns to the movement disorder or neurologic center, where frequency, voltage, and pulse width parameters are configured in accordance with the patient's symptoms. Possible complications of DBS include medical issues such as myocardial infarction, pneumonia, deep vein thrombosis, and pulmonary embolism and surgical issues such as cerebral hematoma, stroke, seizures, infections, and hardware dysfunction, all reported in a small percentage of patients. Side effects may include paresthesia, dysarthria, ataxia, and mood dysregulation, which are typically reversible and ameliorated by changing the stimulation parameters.

KEY POINTS

- **The aim of Parkinson disease treatment is to optimize on time and reduce off time while minimizing troublesome levodopa-induced dyskinesia. Treatment of levodopa-induced dyskinesia requires identifying its occurrence in relation to levodopa dosing.**
- **Surgical treatment of Parkinson disease was developed for patients who, despite medication optimization, experience motor symptoms that cannot be satisfactorily ameliorated by medication.**

OFFICE VISIT

Patients with Parkinson disease will most likely visit a neurology or movement disorder specialist for treatment. Health care providers must pay attention to both motor and nonmotor symptoms of the disease. Information about any recent falls, swallowing issues, comorbid conditions, hospitalizations, or a change in living arrangements should be obtained. Nonmotor symptoms including constipation, pain, and mood disorders should not be neglected (refer to the section on nonmotor symptoms). Patients should be encouraged to visit their primary care physicians and other specialists for general health and psychiatric care.

Medication Adjustment for Motor Function

When evaluating a patient with Parkinson disease for medication adjustment, it is important to remember that this is a disease of timing. Failure to understand a patient's motor and nonmotor response to his or her medication schedule throughout the entire day may preclude precise medication adjustments from being made. Rarely will this information be obtained by simply calculating the total daily dose of Parkinson disease medications or asking general questions, such as "How are you doing?" or "Are you having any problems?" Patient diaries, indicating the times medications are taken and the clinical response throughout a 24-hour period are usually very helpful in obtaining a pattern of motor responses to medications.

Medication adjustments may begin after taking an account of Parkinson disease medications and the times they are dosed. The creation of a lined chart may be helpful. The number of doses taken throughout the day should be filled in

the table according to when the patient reports they are taken. Attention should be paid to whether the medications have been given in immediate-release or controlled-release forms.

Questions regarding motor response may include the following:

- **How much time does it take for your Parkinson disease medications to take effect after each dose?**
- **How long does the effect of each medication last? (Record this information for each dose interval.)**
- **Do you develop dyskinesia during the mid-dose period? Does dyskinesia occur toward the beginning or end of the dose interval?**
- **Do you experience wearing off toward the end of the dose interval? Can you estimate how long this occurs before the next dose begins?**
- **Do you experience early morning dystonia or pain or curling in your limbs? Does dystonia occur at other times during the day?**
- **Do you have periods of the day when your medications do not seem to work? Do these periods occur around meal times?**

Armed with this information, changes to medication dosing may be tailored to provide maximum on time and minimum off time. For example, if predictable wearing off occurs, the medication dose may need to be increased or given more frequently or another formulation of carbidopa/levodopa may be used. If early morning dystonia occurs, patients may benefit from a carbidopa/levodopa controlled release at bedtime. If patients report lack of medication efficacy after a protein meal, they might be counseled to eat smaller doses of protein throughout the day. Bothersome dyskinesia may also be treated with an NMDA antagonist or by redistributing carbidopa/levodopa.

CONCLUSION

Parkinson disease is a complex neurodegenerative disease that appears to be a heterogeneous disorder. Exciting research continues to take place regarding the etiology and pathogenesis of the disease. Novel neuroimaging techniques such as SPECT scans may now assist with disease diagnosis. New formulations of Parkinson disease medications are available for easier administration and improved clinical efficacy.

Treatment of Parkinson disease continues to be symptomatic, however, and the disease cannot yet be cured. The realization that Parkinson disease has a preclinical phase has prompted the need for early biomarkers. Research continues to focus on neuroprotective and disease-modifying strategies, including therapies targeting α-synuclein. Future research in the etiology, pathophysiology, and ultimately a cure for Parkinson disease remains hopeful, considering the remarkable progress made in the last half century.

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VIDEO LEGENDS

VIDEO 1-1
Parkinson disease. Video shows a 67-year-old man with Parkinson disease exhibiting resting tremor of his right arm and decreased arm swing during gait testing.
links.lww.com/CONT/A348

VIDEO 1-2
Dyskinesia. Video shows a 67-year-old man with advanced Parkinson disease exhibiting involuntary choreiform movements in his limbs, neck, and torso, consistent with levodopa-induced dyskinesia.
links.lww.com/CONT/A349

VIDEO 1-3
Dystonia. Video shows a 64-year-old man with advanced Parkinson disease, off carbidopa/levodopa, exhibiting involuntary dorsiflexion of his feet, consistent with "off" dystonia.
links.lww.com/CONT/A350

REFERENCES

1 Hirtz D, Thurman DJ, Gwinn-Hardy K, et al. How common are the "common" neurologic disorders? Neurology 2007:68(5):326–327. doi:10.1212/01.wnl.0000252807.38124.a3.

2 Parkinson J. An essay on the shaking palsy. London: Whittingham and Rowland Sherwood, Neely and Jones, 1817.

3 Charcot JM. Lectures on the diseases of the nervous system, delivered at La Salpetriere. London: The New Sydenham Society, 1877.

4 Carlsson A, Lindqvist M, Magnusson T. 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. Nature 1957;180(4596):1200. doi:10.1038/1801200a0.

5 Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of Parkinsonism. N Engl J Med 1967;282(7):31–33. doi:10.1056/NEJM196702162760703. doi:10.1056/NEJM196702162760703.

6 Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. Neurology 2001;56(11 suppl 5):S1–S88. doi:10.1212/WNL.56.suppl_5.S1.

7 Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001;16(3):448–458. doi:10.1002/mds.1090.

8 Cell Signaling Technology. Cell Signaling Technology web site. Dopamine signaling in Parkinson's disease interactive pathway. *cellsignal.com/reference/pathway/parkinsons_disease.html.* Accessed June 9, 2019.

9 Nussbaum RL, Ellis CE. Alzheimer's disease and Parkinson's disease. N Engl J Med 2003;348:1356–1364.

10 de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. Lancet Neurol 2006;5(6):525–535. doi:10.1016/S1474-4422(06)70471-9.

11 Elbaz A, Bower JH, Maraganore DM, et al. Risk tables for parkinsonism and Parkinson's disease. J Clin Epidemiol 2002;55(1):25–31. doi:10.1016/S0895-4356(01)00425-5.

12 Taylor KS, Cook JA, Counsell CE. (2007) Heterogeneity in male to female risk for Parkinson's disease. J Neurol Neurosurg Psychiatry 78(8):905–906. doi:10.1136/jnnp.2006.104695.

13 Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 2008;79(4):368–376. doi:10.1136/jnnp.2007.131045.

14 Obeso J, Stamelou M, Geotz CG, et al. Past, present, and future of Parkinson's disease: a special essay on the 200th anniversary of the shaking palsy. Mov Disord 2017;32(9):1264–1310. doi:10.1002/mds.27115.

15 Samii A, Nutt JG, Ransom BR. Parkinson's disease. Lancet 2004;363(9423):1783–1793. doi:10.1016/S0140-6736(04)16305-8.

16 Berardelli A, Rothwell JC, Thompson PD, Hallett M. Pathophysiology of bradykinesia in Parkinson's disease. Brain 2001;124(pt 11):2131–2146. doi:10.1093/brain/124.11.2131.

17 Luquin MR, Scipioni O, Vaamonde J, et al. Levodopa-induced dyskinesias in Parkinson's disease: clinical and pharmacological classification. Mov Disord 1992:7(2):117–124. doi:10.1002/mds.870070204.

18 Tolosa E, Compta Y. Dystonia in Parkinson's disease. J Neurol 2006;253(suppl 7):vii7–vii13. doi:10.1007/s00415-006-7003-6.

19 Aquino CC, Fox SH. Clinical spectrum of levodopa-induced complications. Mov Disord 2015;30(1):80–89. doi:10.1002/mds.26125.

20 Morgan JC, Fox SH. Treating the motor symptoms of Parkinson disease. Continuum (Minneap Minn) 2016;22(4):1064–1085. doi:10.1212/CON.0000000000000355.

21 Giladi N, Nieuwboer A. Understanding and treating freezing of gait in parkinsonism, proposed working definition, and setting the stage. Mov Disord 2008;23(suppl 2):S423–S425. doi:10.1002/mds.21027.

22 Chaudhuri KR, Healy DG, Schapira AH; National Institute for Clinical Excellence. Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 2006;5(3):235–245. doi:10.1016/S1474-4422(06)70373-8.

23 Storch A, Schneider CB, Wolz M, et al. Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. Neurology 2013;80(9):800–809. doi:10.1212/WNL.0b013e318285c0ed.

24 Pfeiffer RF. Management of autonomic dysfunction in Parkinson's disease. Semin Neurol 2017;37(2):176–185. doi:10.1055/s-0037-1601568.

25 Goldman JG, Postuma R. Premotor and nonmotor features of Parkinson's disease. Curr Opin Neurol 2014;27(4):434–441. doi:10.1097/WCO.0000000000000112.

26 Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30(12):1591–1601. doi:10.1002/mds.26424.

27 Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson's disease. Arch Neurol 1999;56(1):33–39. doi:10.1001/archneur.56.1.33.

28 Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55(3):181–184. doi:10.1136/jnnp.55.3.181.

29 Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51(6):745–752. doi:10.1136/jnnp.51.6.745.

30 Berg D, Lang AE, Postuma RB, et al. Changing the research criteria for the diagnosis of Parkinson's disease: obstacles and opportunities. Lancet Neurol 2013;12(5):514–524. doi:10.1016/S1474-4422(13)70047-4.

31 Stern MB, Lang A, Poewe W. Toward a redefinition of Parkinson's disease. Mov Disord 2012;27(1):54–60. doi:10.1002/mds.24051.

32 Kempster PA, Williams DR, Selikhova M, et al. Patterns of levodopa response in Parkinson's disease: a clinico-pathological study. Brain 2007;130(pt 8):2123–2128. doi:10.1093/brain/awm142.

33 McFarland NR, Hess CW. Recognizing atypical Parkinsonisms: "Red Flags" and therapeutic approaches. Semin Neurol 2017;37(2):215–227. doi:10.1055/s-0037-1602422.

34 Hirsch E, Graybiel AM, Agid YA. Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. Nature 1988;334(6180):345–348. doi:10.1038/334345a0.

35 Lang AE, Obeso JA. Time to move beyond nigrostriatal dopamine deficiency on Parkinson's disease. Ann Neurol 2004;55(6):761–765. doi:10.1002/ana.20102.

36 Nutt JG. Motor subtype in Parkinson's disease: different disorders or different stages of disease? Mov Disord 2016;31(7):957–961. doi:10.1002/mds.26657.

37 Gan-Or Z, Liong C, Alcalay RN. GBA-associated Parkinson's disease and other synucleinopathies. Curr Neurol Neurosci Rep 2018;18(8):44. doi:10.1007/s11910-018-0860-4.

38 Mazzulli JR, Xu YH, Sun Y, et al. Gaucher disease glucocerebrosidase and α-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell 2011;146:37–52. doi:10.1016/j.cell.2011.06.001.

39 Hauser RA, Grosset DG. [123I]FP-CIT (DaTscan) SPECT brain imaging in patients with suspected parkinsonian syndromes. J Neuroimaging 2012;22(3):225–230. doi:10.1111/j.1552-6569.2011.00583.x.

40 Benamer TS, Patterson J, Grosset DG, et al. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group. Mov Disord 2000;15(3):503–510. doi:10.1002/1531-8257(200005)15:3<503::AID-MDS1013>3.0.CO;2-V.

41 Benamer HT, Oertel WH, Patterson J, et al. Prospective study of presynaptic dopaminergic imaging in patients with mild parkinsonism and tremor disorders: part 1. Baseline and 3-month observations. Mov Disord 2003;18(9):977–984. doi:10.1002/mds.10482.

42 Asenbaum S, Pirker W, Angelberger P, et al. [123I] beta-CIT and SPECT in essential tremor and Parkinson's disease. J Neural Transm (Vienna) 1998;105(10–12):1213–1228. doi:10.1007/s007020050124.

43 Jennings DL, Seibyl JP, Oakes D, et al. (123I) beta-CIT and single-photon emission computed tomographic imaging vs clinical evaluation in Parkinsonian syndrome: unmasking an early diagnosis. Arch Neurol 2004;61(8):1224–1229. doi:10.1001/archneur.61.8.1224.

44 Pagano G. Niccolini F, Politis M. Imaging in Parkinson's disease. Clin Med (Lond) 2016;16(4):371–375. doi:10.7861/clinmedicine.

45 Fahn S, Elton RL, UPDRS program members. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. Recent developments in Parkinson's disease, vol. 2. Florham Park, NJ: Macmillan Healthcare Information, 1987:153–163, 293–304.

46 Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008;23(15):41–47. doi:10.1002/mds.22340.

47 Goetz CG, Nutt JG, Stebbins GT. The Unified Dyskinesia Rating Scale: presentation and clinimetric profile. Mov Disord 2008;23(16): 2398–403. doi:10.1002/mds.22341.

48 Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967;17(5): 427–442.

49 Schwab RS, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson MC, editors. Third symposium on Parkinson's disease. Edinburgh: Livingston, 1969:152–157.

50 Zhang JL, Chan P. Reliability and validity of PDQ-39: a quality-of-life measure for patients with PD in China. Qual Life Res 2012;21(7): 1217–1221. doi:10.1007/s11136-011-0026-1.

51 Storch A, Schneider CB, Klingelhöfer L, et al. Quantitative assessment of non-motor fluctuations in Parkinson's disease using the Non-Motor Symptoms Scale (NMSS). J Neural Transm (Vienna) 2015;122(12):1673–1684. doi:10.1007/s00702-015-1437-x.

52 Hauser RA, Friedlander J, Zesiewicz TA, et al. A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. Clin Neuropharmacol 2000;23(2): 75–81.

53 Rodríguez-Molinero A, Pérez-López C, Samà A, et al. A kinematic sensor and algorithm to detect motor fluctuations in Parkinson disease: validation study under real conditions of use. JMIR Rehabil Assist Technol 2018;5(1):e8. doi:10.2196/rehab.8335.

54 Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004;351(24):2498–2508. doi:10.1056/NEJMoa033447.

55 Hauser RA, Hsu A, Kell S, et al. Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial. Lancet Neurol 2013;12(4):346–356. doi:10.1016/S1474-4422(13)70025-5.

56 Morgan JC, Dhall R, Rubens R, et al. Dosing patterns during conversion to IPX066, extended-release carbidopa-levodopa (ER CD-LD), in Parkinson's disease with motor fluctuations. Parkinsons Dis 2018;2018:9763057. doi:10.1155/2018/9763057.

57 Fernandez HH, Odin P. Levodopa-carbidopa intestinal gel for treatment of advanced Parkinson's disease. Curr Med Res Opin 2011; 27(5):907–919. doi:10.1185/03007995.2011.560146.

58 Wirdefeldt K, Odin P, Nyholm D. Levodopa-carbidopa intestinal gel in patients with Parkinson's disease: a systematic review. CNS Drugs 2016;30(5):381–404. doi:10.1007/s40263-016-0336-5.

59 Onofrj M, Bonanni L, Cossu G, et al. Emergencies in parkinsonism: akinetic crisis, life-threatening dyskinesias, and polyneuropathy during L-Dopa gel treatment. Parkinsonism Relat Disord 2009; 15(suppl 3):S233–S236. doi:10.1016/S1353-8020(09)70821-1.

60 Deleu D, Northway MG, Hanssens Y. Clinical pharmacokinetic and pharmacodynamic properties of drugs used in the treatment of Parkinson's Disease. Clinical Pharmacokinet 2002;41(4):261–309. doi:10.2165/00003088-200241040-00003.

61 Olanow CW, Watkins PB. Tolcapone. Clin Neuropharmacol 2007;30(5):287–294. doi:10.1097/wnf.0b013e318038d2b6.

62 Truong DD. Tolcapone: review of its pharmacology and use as adjunctive therapy in patients with Parkinson's disease. Clin Interv Aging 2009;4:109–113. doi:10.2147/CIA.S3787. PMC 2685232.

63 Valeant Pharmaceuticals International. Tasmar (tolcapone). *www.accessdata.fda.gov/drugsatfda_docs/label/2006/020697s010lbl.pdf*. Accessed June 7, 2019.

64 Stocchi F, Arnold G, Onofrj M, et al. Improvement of motor function in early Parkinson disease by safinamide. Neurology 2004;63(4): 746–748. doi:10.1212/01.WNL.0000134672.44217.F7.

65 Pahwa R, Tanner CM, Hauser RA, et al. Amantadine extended release for levodopa-induced dyskinesia in Parkinson's disease (EASED Study). Mov Disord 2015;30(6):788–795. doi:10.1002/mds.26159.

66 Olanow CW. Levodopa: effect on cell death and the natural history of Parkinson's disease. Mov Disord 2015;30(1):37–44. doi:10.1002/mds.26119.

67 Cilia R, Akpalu A, Sarfo FS, et al. The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. Brain 2014;137(pt 10):2731–2742. doi:10.1093/brain/awu195.

68 Espay AJ, Lang AE. Common myths in the use of levodopa in Parkinson's disease: when clinical trials misinform clinical practice. JAMA Neurol 2017;74(6):633–634. doi:10.1001/jamaneurol.2017.0348.

69 Ahlskog E. Aerobic exercise: evidence for a direct brain effect to slow Parkinson disease progression. Mayo Clin Proc 2018;93(3):360–372. doi:10.1016/j.mayocp.2017.12.015.

70 Lewitt PA. Levodopa for the treatment of Parkinson's disease. N Engl J Med 2008;359(23): 2468–2476. doi:10.1056/NEJMct0800326.

71 Benabid AL, Pollak P, Seigneuret E, et al. Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. Acta Neurochir Suppl (Wien) 1993;58: 39–44. doi:10.1007/978-3-7091-9297-9_8.

72 DeLong MR, Huang KT, Gallis J, et al. Effect of advancing age on outcomes of deep brain stimulation for Parkinson disease. JAMA Neurol 2014;71(10):1290–1295. doi:10.1001/jamaneurol.2014.1272.

73 Bari AA, Thum J, Babayan D, Lozano AM. Current and expected advances in deep brain stimulation for movement disorders. Prog Neurol Surg 2018; 33:222–229. doi:10.1159/000481106.

74 Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368(7):610–622. doi:10.1056/NEJMoa1205158.