Diagnosis and Management of Parkinson's Disease

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Abstract

Despite numerous efforts to identify specific and sensitive biomarkers, the diagnosis of Parkinson's disease (PD) is still based on clinical criteria that include the presence of a combination of cardinal motor features (tremor, rigidity, bradykinesia, and postural instability), other motor features (including freezing of gait and abnormal postures), and numerous nonmotor features. In addition, the presence of atypical features may suggest an alternative diagnosis. Levodopa therapy remains the gold standard in the management of motor features of PD. New formulations of levodopa and novel delivery systems are currently being evaluated and gradually introduced in clinical practice in an attempt to prevent or treat levodopa-related motor complications. Dopamine agonists also play an important role as monotherapy in mild or adjunctive therapy in moderately advanced disease. As the disease progresses and patients develop complications from levodopa therapy, specifically motor fluctuations and dyskinesias, deep brain stimulation becomes an alternative therapeutic option. Clinical trials of experimental therapeutics are currently fueling the PD therapeutic pipeline.

Keywords

- Parkinson's disease
- motor fluctuations
- dyskinesia
- levodopa
- deep brain stimulation

Diagnosis of Parkinson's Disease

In his classic *Essay on the Shaking Palsy* published 200 years ago, James Parkinson described the characteristic features of the disease that now bears his name.[1] Despite efforts directed toward the development of diagnostic tools or disease-specific biomarkers, the diagnosis of Parkinson's disease (PD) still rests on the observation of typical clinical features; there is no specific diagnostic test for the disease.[2–5]

Several nonmotor symptoms have been identified early in the course of PD, some of which may precede the onset of motor symptoms. These include rapid eye-movement sleep behavior disorder (RBD), hyposmia or anosmia, constipation, daytime somnolence, symptomatic hypotension, erectile dysfunction, urinary dysfunction, and depression (►**Table 1**).[2] In addition to nonmotor features, proposed markers of prodromal PD include a score of > 3 on the Unified Parkinson's Disease Rating Scale (UPDRS) or > 6 on the International Parkinson and Movement Disorder Society (MDS) version of the UPDRS (MDS-UPDRS) with exclusion of postural and action tremor scores, abnormal presynaptic dopaminergic uptake by single photon emission computed tomography or positron emission tomography, and consideration of several risk markers (e.g., male gender, occupational solvent or pesticide exposure, and family history).[2]

The relatively high diagnostic accuracy of PD, based on clinical criteria, is supported by a review of 11 clinicopathological studies in which findings from autopsied brains of patients with PD were the gold standard for diagnosis.[5] The pooled diagnostic accuracy was 80.6%; the accuracy for clinical diagnosis performed by movement disorders experts rose from 79.6% at initial assessment to 83.9% at follow-up. Historically, the UK Brain Bank Criteria have been the most widely used diagnostic criteria for PD, but because of changing concepts about PD, including the recognition of nonmotor symptoms as essential elements of the disease, the MDS set up a task force to propose a set of diagnostic criteria for clinically established and probable PD intended to standardize its

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Table 1 Clinical features of Parkinson's disease

Motor features	Nonmotor features
Cardinal features	Hyposmia
Bradykinesia	Pain
Tremor	Sleep disturbances
Rigidity	REM sleep behavior disorder
Postural instability	Insomnia
Other features	Daytime somnolence
Freezing of gait	Neuropsychiatric disturbances
Flexed posture	Mood disturbance (depression, anxiety, apathy)
	Impulse control disorders
	Cognitive impairment (loss of verbal fluency, executive function, and visuospatial capacity)
	Autonomic dysfunction
	Gastrointestinal dysfunction (dysphagia, sialorrhea, gastroparesis, constipation) Genitourinary dysfunction (overactive bladder, erectile dysfunction)
	Sweating dysfunction (hyperhidrosis or hypohidrosis)

Abbreviations: REM, rapid eye movement.

diagnosis.[4] The diagnosis of PD based on these MDS criteria requires parkinsonism (bradykinesia with either rigidity, rest tremor, or both) in conjunction with both supportive features (including clear benefit with dopaminergic therapy, presence of levodopa-induced dyskinesias, observed or documented rest tremor, and olfactory loss or cardiac sympathetic denervation by metaiodobenzylguanidine [MIBG scintigraphy] and the absence of exclusion criteria and "red flags"; ►**Table 2**). A person can be considered to have clinically established PD (at least 90% specificity) with the presence of at least two supportive criteria, absence of absolute exclusion criteria, and no red flags; or clinically probable PD (at least 80% specificity) with the absence of absolute exclusion criteria, and the presence of supportive criteria at least equal in number to the red flags present.[4] The validation of these rather complex clinical criteria is still ongoing, but ultimately, the definite diagnosis of PD rests on the pathological features noted on an autopsy examination of the brain.[6,7] There is, however, an ongoing debate whether PD should be defined by clinical, pathological, or genetic criteria, possibly supplemented by neuroimaging and biochemical data.[8]

To complicate the diagnostic process further is the acknowledgment that PD is not a uniform disorder and that there are different forms and subtypes of PD. The two major clinically defined subtypes of PD, tremor-dominant PD and postural instability gait difficulty form of PD, suggest that PD patients who present with tremor as the dominant clinical feature tend to have a slower progression, better response to dopaminergic drugs, and overall a better prognosis than those with the postural instability gait difficulty phenotype.[9] Besides these two subtypes, other categories of PD have been proposed and are being further characterized, but they need to be validated by clinical, pathological, and imaging methods.[10–12]

Table 2 Red flags in the diagnosis of Parkinson's disease[4]

Rapid progression of gait impairment requiring regular use of a wheelchair within 5 years of onset.
Complete absence of progression of motor symptoms or signs over 5 or more years unless stability is related to treatment.
Early bulbar dysfunction, defined as one of severe dysphonia, dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft foot, nasogastric tube, or gastrostomy feeding) within the first 5 years of disease.
Inspiratory respiratory dysfunction defined as either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs.
Severe autonomic failure in the first 5 years of disease.
Recurrent falls because of impaired balance within 3 years of onset.
The presence of disproportionate anterocollis (dystonic in nature) or contractures of hands or feet within the first 10 years.
Absence of any of the common nonmotor features of disease despite 5-year disease duration.
Otherwise unexplained pyramidal tract signs defined as pyramidal weakness or clear pathologic hyperreflexia.
Bilateral symmetric parkinsonism throughout the disease course.

In addition to phenomenological characterization of clinical features of PD, there is also growing interest in better assessment tools for the various motor and nonmotor features of PD. Although the UPDRS and the MDS-UPDRS are very useful clinical scales, employed in numerous clinical trials, and supplemented by a variety of quality-of-life measures, there is an unmet need to develop more objective and quantitative methods designed to assess the severity of the disease and its impact on gross and fine motor functioning, gait, balance, and other features.[13–15] It is not clear, however, whether the various wearables, quantitative instruments, and other developing technologies will translate into more meaningful assessments of PD patients and improve clinical management. They may possibly be useful in the development of various objective biomarkers used in the early detection of the disease and in the longitudinal tracking of patients with PD.[16,17] Currently, these new technologies are primarily explored as research tools, but eventually may be adopted in daily clinical care. When coupled with new imaging techniques, analyses of cerebrospinal fluid, and biopsies of skin and other tissues to search for synuclein pathologies, these novel techniques will incrementally advance our ability to detect PD, even in the prodromal stage.[18–20]

Motor Features

Bradykinesia

Bradykinesia, or slowness of movement, is the most characteristic feature of PD. Bradykinesia may be manifested by hypokinesia (small amplitude of movements) and akinesia (paucity or absence of movements). This can initially present as reduced blinking or decreased facial expression (hypomimia), excess saliva or drooling (due to impaired swallowing), hypophonic speech, perceived clumsiness or difficulty with fine motor control, slowness in performing activities of daily living, or reduced arm swing when walking.[21–23] Screening for other causes of slowed movement, including weakness, or diminished effort (as may be seen in depression) is important. The assessment of bradykinesia on examination should include having the patient perform as rapidly as possible repetitive movements (such as finger taps, toe taps, and opening and closing hands) and assess for slowness and decrementing amplitude. Attention should be paid to other evidence of bradykinesia (gesturing, facial expressions, blinking, speech, arm swing while walking) throughout the history and examination.

Tremor

The characteristic tremor of PD is a 4 to 6 Hz supination-pronation "pill rolling" hand tremor that typically occurs at rest. This classic rest tremor should be distinguished from primarily action (postural or kinetic) tremor, which may also occur in patients with PD, but is more characteristic of essential tremor (ET), often confused with PD. Rest tremor associated with PD is typically present in the hands, lips, chin, jaw, and legs, but if the patient manifests head, voice, or handwriting tremor, one should consider the diagnosis of ET alone or in combination with PD. Indeed, some patients may have ET for years or decades before the onset of PD, but the pathogenic relationship between the two conditions is not well understood.[24] In addition to rest and postural tremor, patients with PD often describe "internal tremor," a tremulous sensation without visible tremor, reported in 31 to 44% of PD patients.[25] Assessment of tremor should include observation of tremor at rest with limbs in a relaxed position and while the patient is walking, as well as evaluation of postural tremor (with maneuvers such as having the patient extend his or her arms in a horizontal position in front of the body and in a "wing-beating" position) and kinetic tremor (with maneuvers such as finger-to-nose testing). Many patients with rest tremor also have a re-emergent tremor, in which the postural tremor does not appear for seconds or minutes after assuming antigravity posture with arms outstretched in front of the body or in a wing-beating position.[26] The frequency of this tremor is identical to that of the rest tremor in PD, thus providing evidence that this re-emergent tremor is pathophysiologically linked to the typical rest tremor of PD.[26] This is in marked contrast to ET, in which the postural tremor occurs immediately (without latency) after assuming the horizontal posture. Typical supinating-pronating or re-emergent tremor can also be seen when the patients are walking, during which the rest tremor is often markedly exacerbated. Vigilant observation of the patient throughout the history and examination is critical to identifying rest and other tremors associated with PD and differentiating these tremors from those of ET or other tremors.[24]

Rigidity

Rigidity is characterized by a continuous and uniform increased resistance to movement (so-called lead pipe resistance). This sign can often manifest as pain, typically in the shoulder or other limb pain, an often-overlooked symptom that can precede more overt clinical signs of PD by several years.[27–29] Indeed, rigidity-related pain is one of many sensory symptoms associated with PD. Examination of a patient with PD should include an evaluation of both axial (neck and trunk) and peripheral (limb) rigidity through passive movement. Although rigidity may not be apparent initially, the use of activating maneuvers of the contralateral limb (also known as Froment's maneuver), may unmask otherwise unappreciated rigidity.[30] The presence of "cogwheeling" may be seen when both rigidity and tremor are present in a limb, although cogwheeling can be detected in some patients with PD without any evidence of tremor or rigidity. This persistent uniform resistance to passive movement through the full range of motion of the joint should be distinguished from velocity dependent spasticity, and the impaired relaxation of paratonia or gegenhalten.[30]

Postural Instability

Postural instability is typically a feature of more advanced PD, though it is still considered one of the four cardinal motor features of the disease. This instability is the result of a loss of both automatic postural reactions (in response to visual, vestibular, and somatosensory inputs), and anticipatory postural adjustments (associated with voluntary movements to mitigate anticipated postural disturbances preceding their onset).[31] Additional contributions to postural instability include

orthostatic hypotension, freezing, and even fear of falling.[32] Postural instability can be assessed on examination using the pull test, consisting of a patient being briskly pulled backward from the shoulders; variations of this test include a push and release test and an unexpected shoulder pull test.[33–35]

Other Motor Features

Though not considered one of the four cardinal features, freezing of gait is a characteristic and often the most disabling feature of PD, typically more prominent in later stages of the disease.[36] Several types of freezing of gait have been recognized: start hesitation (with initiation of walking), turn hesitation (when feet appear to become stuck when making a turn), hesitation in tight quarters (such as through a doorway), destination hesitation (freezing as a patient approaches a target), and open space hesitation (seemingly spontaneous freezing).[37] Patients often make the observation that listening to marching music or some other rhythmic sound can help them overcome freezing.[38] Because this PD symptom usually does not respond well to dopaminergic or other drugs, patients and their physical therapies use a variety of "tricks" to help them prevent or cope with freezing, such as visual cues, high-steppage marching gait, and other maneuvers.

A stooped posture (with neck, truncal, elbow, and knee flexion) is widely recognized as a feature of PD. In some cases, the neck and truncal flexion can be quite severe resulting in bent spine syndrome or camptocormia.[39] Additional postural abnormalities including striatal hand (involving flexion of the metacarpophalangeal joints and extension of the interphalangeal joints) as well as striatal toe (flexion or extension of the toes), scoliosis, and truncal tilt (also known as Pisa syndrome) have been described in about a third of PD patients. Joint and postural abnormalities have been generally associated with an earlier age at onset and more rapid progression of the disease.[40]

Nonmotor Features

Parkinson's disease has been traditionally considered a motor disorder, but there are several nonmotor symptoms that have been identified and highlighted in recent reviews as characteristic features of PD or as manifestations of levodopa-related fluctuations.[41–46]

Hyposmia or anosmia is an associated feature of PD that has been shown both clinically and pathologically to often predate the onset of motor symptoms by years or decades, and is present in 80% of patients with PD.[47,48] Its utility as a diagnostic tool, however, is limited due to the low sensitivity and specificity of testing.[49] Pain is a frequent complaint among patients with PD, with one study estimating the prevalence at 83%.[28,50]

Rapid eye-movement (REM) sleep behavior disorder, manifested by acting out dreams with a loss of normal atonia during REM sleep, can also predate the onset of motor symptoms by many years, or occur at any point during the disease.[51] Although the gold standard for its diagnosis is polysomnography, one study showed that a single question, "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (e.g., punching, flailing your arms in the air, making running movements, etc.)?" had over 90% specificity and sensitivity for detecting RBD.[52] It is important to note that RBD may be even more prevalent in other synucleinopathies, such as multiple system atrophy, and has been associated with other neurodegenerative diseases.[53] Other sleep disturbances in part linked to the presence of RBD include daytime somnolence and insomnia due to fragmented sleep.

Neuropsychiatric comorbidities show an increased incidence in patients with PD as compared with the general population, most commonly depression and anxiety, but also apathy, psychosis, and sleep disturbances.[54,55] Impulsive and compulsive behaviors can also be seen at an increased frequency in PD patients both independently and in association with the use of dopaminergic medications, particularly dopamine agonists.[56] Often a prodromal phase of PD can include the development of a mood disorder, such as depression and apathy.[57] Cognitive dysfunction can also be seen in PD, with frequency ranging from 20 to 90%, depending on the method of assessment, diagnostic criteria, and duration of the disease.[58,59] The pattern of deficits is typically seen as executive dysfunction, impaired verbal fluency, and visuospatial and visuoperceptive problems.[60] Cognitive disturbances can have important implications on the approach to management of other symptoms of the disease, as well as a substantial impact on quality of life.[61]

Dysautonomia is well established in PD and can include orthostatic hypotension; gastrointestinal disturbances including weight loss, constipation, and dysphagia; genitourinary disturbances including erectile dysfunction, overactive bladder, and less frequently urinary retention; and thermoregulatory dysfunction including disturbances with sweating.[62] When autonomic symptoms occur early in the course of the disease, precede the motor symptoms, or dominate the clinical disability, the diagnosis of multiple system atrophy should be considered.

Exclusionary Features

Equally important to the diagnosis of PD is to search for atypical features and to exclude other causes of parkinsonism. The International Parkinson and Movement Disorder Society, in their diagnostic criteria for PD, has identified 10 such red flags that if present, should question the diagnosis of PD (►**Table 2**).[4] Other features that may raise concern for atypical parkinsonism include poor response to levodopa, the presence of vertical ophthalmoparesis (characteristic of progressive supranuclear palsy), cerebellar dysfunction (characteristic of multiple system atrophy), and apraxia, alien limb, myoclonus or cortical sensory deficit (characteristic of corticobasal degeneration).[63] Prior or current treatment with dopamine receptor blocking or dopamine-depleting agents (neuroleptics), or exposure to toxins (such as manganese in welders) should also be considered as potential red flags in the diagnosis of PD.

Ancillary Testing

Despite a thorough history and examination, even experienced clinicians may encounter cases where the diagnosis of PD is not clear. In such cases, imaging studies including

magnetic resonance imaging of the brain (to look for alternative causes of symptoms such as multiple system atrophy, progressive supranuclear palsy, vascular parkinsonism, and normal pressure hydrocephalus) may be helpful. Furthermore, specialized functional imaging tests such as [123I]-FP-CIT single photon emission computed tomography imaging (DaTscan) and [18F]dopa positron emission tomography imaging, which can indicate a dopamine deficiency in the striatum, may be useful in differentiating PD from ET[64–66] and from other parkinsonian disorders.[67]

Although PD is considered a sporadic and idiopathic disease, mutations in several genes have been linked to the disease, though collectively these monogenetic forms of PD account for less than 10%, of all PD patients. In cases with a strong family history and late-onset disease, *LRRK2* testing may be indicated, whereas in young-onset disease, *PARK2* (Parkin) testing may be considered.[68] In addition to these two specific monogenetic causes of PD, mutations in the α-synuclein (*SCNA*) and the *TMEM230* genes that have been associated with seemingly typical forms of PD.[69,70]

Management of Parkinson's Disease

The management of PD is complex and involves the treatment of both the motor and nonmotor aspects of the disease in early as well as advanced stages of the disease. Once the diagnosis of PD is established, the decision on when and how to treat can follow a basic algorithm (►**Fig. 1**), but it is critical to emphasize that PD therapy must be individualized and tailored to the specific needs of each patient. In addition to nonpharmacological therapy (e.g., exercise, relaxation techniques), drugs such as monoamine oxidase inhibitors (e.g. selegiline, rasagiline, safinamide), dopamine agonists, and anticholinergic medications are often used if the symptoms are mild. Levodopa therapy is usually instituted once the symptoms become troublesome and begin to interfere with activities of daily living or work. Surgical and experimental therapeutics should be considered as the disease progresses and motor complications (including motor fluctuations and dyskinesias) develop. Although no effective neuroprotective therapies have been found, there are currently several clinical trials designed to

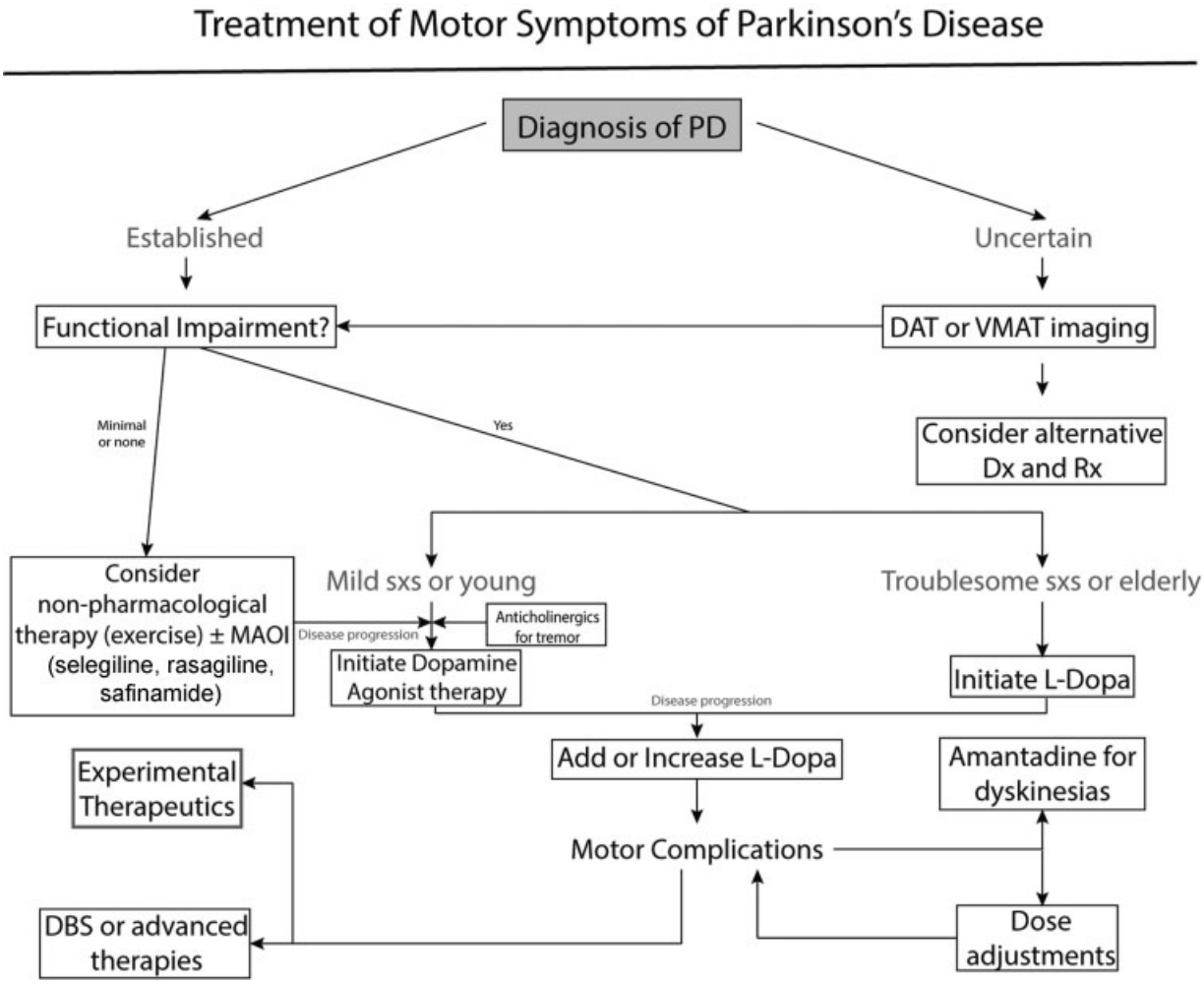

Fig. 1 An algorithm for the management of motor symptoms of Parkinson's disease (PD). Once the diagnosis is established, selected treatment is dependent on a patient's functional impairment, age, and severity of disease. As the disease progresses, addition of levodopa (L-dopa) therapy is necessary. As motor complications develop, management can become more complex, both with more complicated dopaminergic therapy regimens and the use of advanced therapies (such as deep brain stimulation (DBS), intestinal levodopa, or apomorphine) or the consideration of experimental therapies. DAT, dopamine transporter; DX, diagnosis; MAOI, monoamine oxidase inhibitor; RX, treatment; sxs, symptoms; VMAT, vesicular monoamine transporter.

develop potential disease-modifying strategies. In addition to inosine, which increases urates, and isradipine, a calcium channel blocker, there are treatments designed to prevent the accumulation or clear toxic α-synuclein.[71] Until these and other therapies are documented to slow or prevent the progression of the disease, an intensive exercise program is currently recommended as the best approach designed to potentially favorably affect the progression of the disease. In this regard, exercise and physical therapy, particularly resistance and endurance training and other intensive training modalities, have been found most beneficial.[72]

Here we will focus on the treatment of motor symptoms, as nonmotor symptom management, botulinum toxin therapy, deep brain stimulation (DBS) and other surgical treatments are discussed elsewhere in this issue.

Levodopa

Since its introduction in the 1960s, levodopa therapy has remained the gold standard of treatment. Several different formulations of levodopa therapy have been developed over time. Levodopa is typically given in conjunction with a peripheral decarboxylase inhibitor (e.g., carbidopa or benserazide) to inhibit the conversion of levodopa to dopamine in the periphery and thus prevent nausea.[73] When managing a patient with levodopa therapy, the principal issue confronting the clinician is maintaining the patient's symptomatic benefit or "ON" time while avoiding peak-dose dyskinesia, typically in the form of stereotypy (e.g., head bobbing), chorea, dystonia, or myoclonus, as well as minimizing wearing-off effects (recurrence of parkinsonian symptoms).[74] The emergence of these levodopa-related motor complications correlates both with the dose and duration of levodopa therapy, as well as the duration of the disease, with younger-onset patients being at higher risk for developing these complications than patients with late-onset PD.[75] The management of these motor complications often necessitates individual-dose reduction, with an increased frequency of administration to compensate for the relatively short half-life of levodopa.

Several different formulations of levodopa have been developed with the intent to improve the pharmacokinetics of levodopa. The first extended-release formulation of levodopa, Sinemet CR (Merck Co.), developed in the 1980s, has been shown to be effective in prolonging the effects of levodopa, but is associated with erratic absorption, poor or delayed response, and worsening of peak-dose dyskinesias.[73] More recently, the development of another long-acting carbidopa-levodopa (Rytary; Impax Laboratories, Inc.), has been found to reduce motor fluctuations and troublesome dyskinesias, while maintaining "on" time.[76] There is an intestinal gel form of levodopa known as Duopa (AbbVie, Inc. in the United States) or Duodopa (AbbVie, Ltd. in Europe) the goal of which is to eliminate levodopa peaks and troughs through the use of continuous administration via an intestinal pump. In a 12-week, randomized, double-blind, double-dummy trial, involving 66 patients with advanced PD and motor complications, the mean "off" time decreased by 4.04 hour (± 0.65) for patients allocated to the intestinal gel group compared with 2.14 hour (± 0.66) for patients allocated to immediate-release oral group (difference -1.91 hour; $p = 0.0015$).[77] The mean on time without troublesome dyskinesia increased by 4.11 hour (± 0.75) in the intestinal gel group and by 2.24 hour (± 0.76) in the immediate-release oral group (difference 1.86 hour; $p = 0.0059$). This treatment strategy, though quite effective in improving levodopa-related complications is, however, associated with a high complication rate, particularly related to the jejunostomy tube.[78,79] Newer treatments being developed include the use of inhaled levodopa (CVT-301; Acorda Therapeutics), which can be of particular use in rapidly treating motor fluctuations and transdermal formulations.[71,80]

Dopamine Agonists

Dopamine agonists are suitable for use as monotherapy in the management of mild to moderate PD, and are often the first choice of medication in younger patients with the goal of delaying levodopa therapy and the risk of levodopa-induced dyskinesia. Ropinirole, pramipexole, and the transdermally applied rotigotine are the typical dopamine agonists used in the United States. The older, ergot dopamine agonists, such as pergolide and bromocriptine, are no longer used because of increased risk of valvular, pulmonary, and other complications.[81] Apomorphine, delivered through subcutaneous injection, is a rapidly acting dopamine agonist that can be used intermittently to rescue patients from sudden, unpredictable, off periods or as a continuous subcutaneous infusion as a maintenance therapy.[82] Dopamine agonists have also been shown to potentiate the effects of levodopa and can be used in conjunction with levodopa therapy to help enhance and prolong its effects.[83] The side-effect profile of dopamine agonists is in many ways similar to that of levodopa; however, orthostatic hypotension, hallucinations, confusion, somnolence, leg edema, and impulse control disorders are more frequently seen with dopamine agonists.[84] As such, they should be used with caution in older or cognitively impaired patients.

Other Medications

Catechol-O-methyltransferase inhibitors block the peripheral metabolism of levodopa and can be used to extend its duration and enhance its bioavailability.[73,84] This makes it of use in moderate to severe PD in decreasing off time and increasing on time, though its use has been shown to increase the risk of dyskinesias.[85] Selective monoamine oxidase B inhibitors enhance striatal dopaminergic activity by inhibiting the metabolism of dopamine. Although they have been shown to improve motor fluctuations, they are most frequently used early in the course of the disease, when the symptoms are relatively mild and as levodopa-delaying strategies. Studies examining the potential neuroprotective or disease-modifying effects of these medications have produced conflicting and inconclusive data.[86,87] Amantadine can be useful in the management of PD-related tremor and bradykinesia,[88] but is most frequently prescribed to treat levodopa-induced dyskinesias.[89] The use of stimulants such as methylphenidate and atomoxetine may possibly help treat freezing of gait, which can be an otherwise difficult to treat.[90–93] Surgical treatments of PD, such as DBS, will be discussed elsewhere in this volume.

Conclusion

Parkinson's disease is a common and complex disorder both in its diagnosis and management. A thorough understanding of associated symptoms, as well as atypical symptoms, is important for an accurate diagnosis. Levodopa therapy remains the mainstay of treatment, particularly in more advanced/severe disease, though numerous other medications have a role as adjunctive treatment or earlier in the course of the disease. Novel surgical treatments are being investigated not only to provide relief to patients with advanced PD, but to also favorably modify its natural history. Experimental therapeutics in PD provide hope that more effective and safer therapies will be developed in the future to improve the quality of lives of patients with PD, and by targeting key pathogenic mechanisms, to possibly also slow or prevent its progression.[94] Indeed, a phase 1B study of a monoclonal antibody directed at aggregated alpha synuclein in 80 patients with Parkinson's disease provided evidence of strong target engagement and CNS penetration. This supports further clinical studies directed against toxic forms of alpha synuclein.[95]

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